FORMULATION AND PRODUCT DEVELOPMENT OF AZITHROMYCIN TABLETS

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IN

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Submitted by

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CERTIFICATE

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Abbreviations:

NMT	:	Not More Than
NLT	:	Not Less Than
SS	:	Stainless Steel
mg	:	Milligrams
Qty	:	Quantity
MFC	:	Master Formula Card
BMR	:	Batch Manufacturing Record
mm	:	Millimeters
^{o}C	:	Degrees Centigrade
% w/w	:	Percentage weight/weight
QC	:	Quality Control
QA	:	Quality Assurance
BP	:	British Pharmacopoeia
IH	:	In House
USP-NF	:	United State Pharmacopoeia and National formulary
gm	:	Gram
USP	:	United State Pharmacopoeia
N	:	Newton
RH	:	Relative Humidity
Q.S.	:	Quantity sufficient
SOP	:	Standard Operating Procedure
D.T.	:	Disintegration Time
API	:	Active Pharmaceutical Ingredient
Kg	:	Kilogram
IP	:	Indian Pharmacopeia
Ph.Eur	:	European Pharmacopeia
LOD	:	Loss on Drying
NA	:	Not Applicable

CONTENTS

CHAPTER - 1

INTRODUCTION

The main goal of pharmaceutical formulation is to achieve better therapeutic activity in the shortest possible time by using smallest quantity of drug administered by the most suitable route[1].

Drugs can be administered through different routes; however, of all the routes of administration, oral route of administration is most convenient for administering drugs for systemic effect because of ease of administration and dosage adjustments[2]. Parenteral route is not routinely used because of difficulty in self-administration and hence hospitalization may be required. Topical route is recently developed and is employed for only few drugs like nitroglycerine, scopolamine, for systemic effect. Topical route has limitations in its ability to allow effective drug absorption for systemic drug action. Parenteral administration is employed in case of emergency and in which the subject is comatose or cannot swallow. Nevertheless it is possible that at least 90% of all drugs used to produce systemic effect are administered by oral route[3].

Oral route of drug administration has wide acceptable and of the drugs administered orally in solid dosage forms represents the preferred class of products. The reasons are follows: "tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed".

Solid dosage forms of tablets and capsules are more commonly employed, the tablets have advantages than capsules in that they are tamper resistant and any adulterant of the tablet after its manufacture is almost certain to be observed. The adulteration can be easily found if it is done in either liquid form or solid form since deformation takes place, if it is done in liquid form and powders cannot be added to the tablet if once they are formed. The major disadvantage of capsules over tablet is their higher cost. The capsules either hard capsule or soft capsule they are susceptible to breakage if they are not stored properly.

1.1 TABLETS:

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. In European pharmacopoeia tablets are also defined as "Solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volume of particles". They have been in widespread use since the latter part of the 19th century and their popularity continues[1, 2].

Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g.: simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [e.g.: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration].

Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

a) Properties of Tablets[1]:

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistance to shock and abrasion and to withstand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
- The drug content of the tablet must be bioavailability. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels of the drug after its administration.
- Tablets must be elegant in appearance and must have characteristic shape, color, and other markings necessary to identify the product.
- Tablets must retain all these functional attributes, which include drug stability and efficacy.

b) Advantages of Tablets[2]:

- They are easy to administer.
- They are a unit dosage form, and they offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach. Especially when coated, provided that tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large-scale production than other unit oral forms.
- They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamperproof dosage form".

c) Disadvantages of Tablets[2]:

- ❖ Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- ❖ Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
- ❖ Bitter tasting drugs, drugs with objectionable odor or drugs that the sensitive to oxygen or atmosphere moisture may require encapsulation or a special type of coating with may increase the most of the finished tablets.

d) Types of Tablets[1]:

Tablets are classified according to their route of administration or function. The following are the 5 main classification groups:

- **Tablets ingested orally**
  - ✓ Compressed tablets
  - ✓ Multiple compressed tablets
  - ✓ Multilayered tablets
  - ✓ Sustained action tablets
  - ✓ Enteric coated tablets
  - ✓ Sugar coated tablets
  - ✓ Film coated tablets
  - ✓ Chewable tablets
- **Tablets used in the oral cavity**
  - ✓ Buccal tablets
  - ✓ Sublingual tablets
  - ✓ Lozenge tablets and torches
  - ✓ Dental cones
- **Tablets administered by other routes**
  - ✓ Implantation tablets

- ✓ Vaginal tablets

- **Tablets used to prepare solutions**
  - ✓ Effervescent tablets
- **Molded tablets or tablet triturates (TT)**
  - ✓ Dispensing tablets (DT)
  - ✓ Hypodermic tablets (HT)

1.2 TABLET MANUFACTURING[4]:

Tablets are compressed powders and their manufacturing is a complex, multistep process. The ultimate aim is to easily disperse in gastrointestinal fluid and in complete absorption of API and at the same time, offer stability to the formulation.

The tablet manufacturing process can be broadly classified as:

1) Granulation method
   a. Wet granulation method
   b. Dry granulation method
2) Direct compression method

Oral dosage forms mainly solid dosage forms are more popular than other dosage forms but suffer from problems like solubility, absorption Viz. bioavailability, therefore patient compliance. Immediate release/conventional dosage form is one of the approach to achieve the above goal. As dissolution rate is related to absorption and bioavailability, increased dissolution rate will increase absorption to give faster onset of action.

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the challenging aspects of drug development together with the permeability. The solubility behavior of a drug is key determinate of its oral bioavailability. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. The most important property of a dosage form is its ability to deliver the active ingredient to its site of action in an amount sufficient to elicit the desired pharmacological response. This property of the dosage form has been referred to as its physiological availability.

Bioavailability is defined more precisely as the rate and extent of absorption of a drug from its dosage form into the systemic circulation. Accordingly the

absorption of an intravenously administered drug is instantaneous and complete. However, for reasons of convenience and stability, most drugs are administered orally offer first being formulated into dosage forms usually tablets and capsules. The rate and extent of absorption from such dosage forms is usually not precisely known as it is affected by a number of factors related to the drug, dosage form and patient.

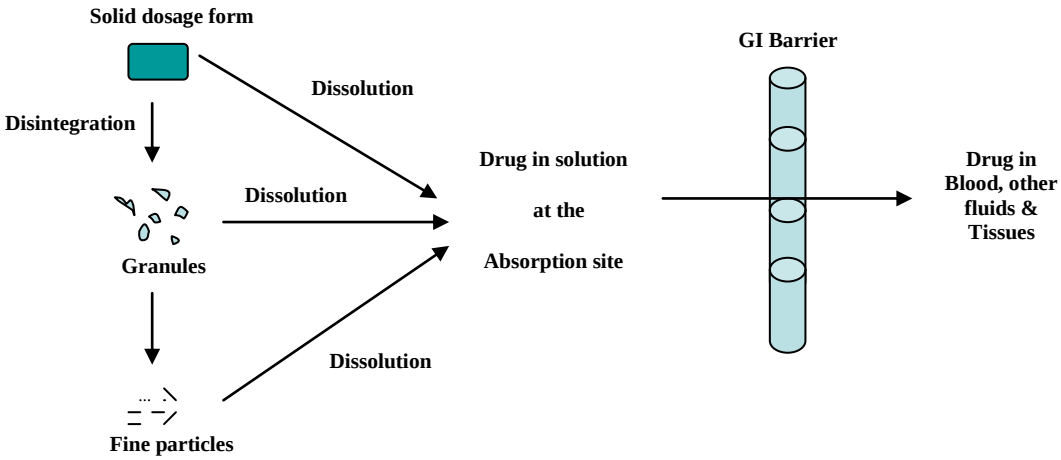


Fig No. 1: Dissolution and Absorption of Drugs from Solid Dosage Forms[3]

When a drug is administered orally in a solid dosage form such as tablet, capsule it must be released from the dosage form and dissolved in the gastro intestinal fluid before it can be absorbed[3]. The bioavailability of many poorly water soluble drugs is limited by their dissolution rates, which are in turn controlled by the surface area that they present for dissolution[6]. Two consecutive transport processes can be identified to describe the oral absorption of drugs from solid dosage forms.

1. Dissolution of the drug in vivo to produce a solution
2. Transport of the dissolved drug across the gastrointestinal membrane.

Each process can be characterized by a rate constant. If the rate of dissolution of the drug is significantly slower than the rate of absorption, the dissolution of the drug becomes the rate-limiting step in the absorption process, and the particle size of the drug is of greater importance in the transport from the gastrointestinal (GI) tract to the site of action Most drugs are passively absorbed and their rates of absorption are dependent upon the concentration gradients in each case; by increasing the dissolution rate in GI tract, the absorption rate increases, so long as the dissolution rate is still the limiting step[5]. This commonly occurs for drugs with limited water solubility.

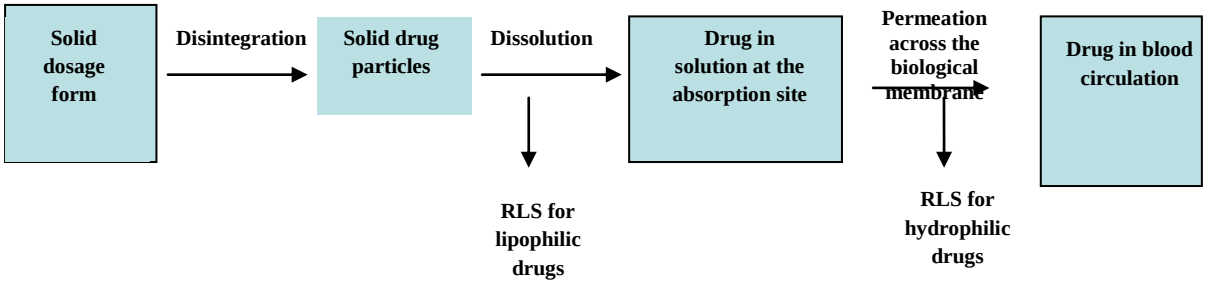


Fig No. 2: The Two Rate limiting Steps in the Absorption of Drugs from orally administered formulations[3]

1.3. THEORIES OF DISSOLUTION:

Dissolution rate may be defined as the amount of drug substance that is dissolved per unit time under standardized conditions of liquid-solid interface, temperature and solvent composition. Dissolution can be considered a specific type of heterogeneous reaction in which a mass transfer results a net effect between the escape and deposition of solute molecules at a solid surface. The most common theory for dissolution, the film theory, also known as the diffusion layer model accepts the assumption that dissolution belongs to a type of heterogeneous reaction where the rate is determined by the transport process[3].

The following is the brief interpretation of this as well as some other important dissolution theories.

a. Noyes-Whitney and Nernst-Brunner Equations:

Noyes* and *Whitney in 1897[6] stated that the rate at which a solid substance dissolved in its own solution is proportional to the difference between the concentration of that solution and the concentration of the saturated solution. Mathematically it can be expressed as

$$\frac{dc}{dt} = K(C_s - C_b)$$

Where: *dc* = the dissolution rate

K = proportionality constant

C_s = the solubility of the solute

C_b = the concentration at any time, t

The ***Noyes - Whitney*** equation can be explained as:

A thin layer of saturated solution is formed at the surface of the solid and the rate of dissolution is governed by the rate of diffusion from this layer to the bulk of the solution. There is negligible change in the surface area with time during dissolutions.

Noyes-Whitney, Brunner[7]* and *Tolloczko[8] revised the equation assuming, that under well-defined conditions of temperature and agitation, the dissolution rate is proportional to the surface area 'S', giving.

$$\frac{dc}{dt} = K_1(C_s - C_b)$$

Where: K_1 = called the intrinsic dissolution rate constant.

Applying ***Fick's law of diffusion*** to *Nernst[9] and Brunner[10] equation*

$$\frac{dc}{dt} = \frac{DS}{hv}(C_s - C_b)$$

Where: ***D*** = the diffusion coefficient of the solute.

h = the thickness of the diffusion layers.

V = the volume of the dissolution medium.

S= surface area

This has been referred to as film theory of ***Nernst Brunner***, which applies to some situations.

b. Cube root law:

Hixson* and *Crowell[12] introduced the concept of changing surface area during dissolution and derived the "**Cube root law**" given by.

$$(W_O)^{1/3} - (W_1)^{1/3} = \left(\frac{\prod NP}{6}\right)^{1/3} \frac{2Dc_s t}{hp}$$

Where: W_0 = the initial weight of solid.

W_1 = the weight of solid at time, t.

N = the number of particles.

P = the density of the solid.

This equation is based on a number of assumptions:

1. Dissolution takes place normal to the surface of the dissolving solid particles.
2. No stagnation of liquid occurs in any region.
3. The same effect of agitation is observed on all areas of the solid surface.
4. Solid particles remain intact during the dissolution process and
5. The stagnant or diffusion layer thickness is independent of the particle diameter

1.4. FACTORS INFLUENCING DRUG ABSORPTION FROM ITS DOSAGE FORM[3,5]:

1. **Pharmaceutical factors:** Include factors relating to the physicochemical properties of the drug and dosage form characteristic and pharmaceutical ingredients.
   a) Physicochemical properties of the drug substances
      - ✓ Drug solubility and dissolution rate
      - ✓ Particle size and effective surface area
      - ✓ Polymorph and amorphism
      - ✓ Pseudo polymorphism
      - ✓ Salt form of the drug
      - ✓ Lipophilicity of the drug
      - ✓ P^{ka} of the drug and pH
      - ✓ Drug stability

   b) Dosage Form Characteristics
      - ✓ Disintegration time
      - ✓ Dissolution time
      - ✓ Manufacturing variables
      - ✓ Pharmaceutical ingredients (excipients / adjuvants)
      - ✓ Nature and type of dosage form
      - ✓ Product and storage conditions
2. **Patient Related Factors:** Include factors relating to the anatomical, physiological and pathological characteristics of the patient
      - ✓ Age
      - ✓ Gastric emptying time
      - ✓ Intestinal transit time
      - ✓ Gastro intestinal pH
      - ✓ Disease states
      - ✓ Blood flow through the GIT
      - ✓ Gastrointestinal contents
      - ✓ Pre-systemic metabolism

1.5. METHODS AVAILABLE TO ENHANCE THE DISSOLUTION RATE:

As far as the definition of bioavailability is concerned, a drug with poor bioavailability is the one with, poor aqueous solubility and / or slow dissolution rate in the biologic fluids, poor stability of the dissolved drug at the physiological p^H, inadequate partition coefficient and thus poor permeation through the bio-membrane and extensive pre-systemic metabolism.

The three major approaches in overcoming the bioavailability problems due to such causes are,

- ✓ The Pharmaceutical Approach
- ✓ The Pharmacokinetic Approach
- ✓ The Biological Approach

1. **The Pharmaceutical Approach:** This involves modification of formulation, manufacturing process or the physicochemical properties of the drug without changing the chemical structure.
2. **The Pharmacokinetic Approach:** In which the pharmacokinetics of the drug is altered by modifying its chemical structure.
3. **The Biological Approach:** Where by the route of administration may be changed such as changing from oral to parentral route.

Methods available to enhance the Dissolution Rate of poorly soluble drugs

Method	Examples of drug
Methods which increases solubility of the drug	
a. Buffering the pH of the environment b. Use of salts of weak acids and bases c. Use of solvates and hydrates d. Use of selected polymorphic forms Complexation e. Pro drug approach f. Use of surfactants	Buffered Aspirin tablets Sodium, potassium and Calcium salts of P-amino salicylic acid Ampicillin hydrate, solvated forms of succinyl sulfathiazole,Novobiocin, Chloramphenicol palmitate Benzocaine – Caffeine complex Prodrugs of Ampicillin in Pirampicillin Hydrocortisone - Tween 80 Tolbutamide - Tween 20
Methods which increase the surface area of the drug.	
a. Micronization (Particle size reduction to increase the surface area) b. Use of surfactants (to increase effective surface area by facilitating proper wetting) c. Solvent deposition (Deposition of poorly soluble drugs on inert materials) d. Solid Dispersions (Dispersion of poorly soluble drug in a solid matrix of water soluble carrier).	Griseofulvin, Digoxin, Phenacetin Phenacetin Oxyphenbutazone, Predinisolone, Indomethacin Griseofulvin – PVP, Reserpine – PVP

DISEASE PROFILE:

1.6 (I) Community Acquired Pneumonia

Definition

Community acquired pneumonia (CAP) refers to a serious infection or inflammation of the lungs that is generally acquired outside of a hospital or long term care facility. When this infection is acquired, the air sacs in your lungs fill with pus or other liquid, making it difficult for oxygen to penetrate through your lungs to reach your bloodstream. If CAP is not treated properly with antibiotics or spreads throughout your body, it can result in death, especially in the elderly or in people with weakened immune systems

Causes

Community acquired pneumonia is spread by close person-to-person contact—usually when an infected person coughs or sneezes on another person. CAP can be caused by several different organisms, including bacteria, viruses, and fungi. The most common organism responsible for CAP is the bacterium known as ***Streptococcus pneumoniae***. Although several "bugs" or organisms have been confirmed to be causes of CAP, about 30% to 50% of pneumonia cases are reported to have an unknown cause—meaning the exact "bug" responsible for the infection is unknown or is not identified via laboratory testing.

About CAP

In the United States, CAP (combined with influenza or "the flu") is the eighth leading cause of death and the number one cause of death from infectious diseases. It is estimated that approximately 5.6 million cases of CAP occur annually and of these 1.1 million require hospitalization. Anyone can be susceptible to CAP, but it more commonly occurs in very young (less than 2 years of age) or elderly people. CAP is also more common in people who smoke or have other severe illnesses, such as chronic obstructive pulmonary disease (COPD), alcoholism, cancer, organ transplants, kidney disease, and immune system disorders.

Risk Factors

Risk factors are characteristics that may increase the chance for developing a condition. The more risk factors present, the more likely you are to develop the condition. You are at an increased risk for developing CAP if you:

- Are 65 years or older
- Have other medical conditions or a combination of conditions such as:

1. Chronic obstructive lung disease (COPD) or other chronic lung disorders
2. Diabetes mellitus
3. Chronic kidney disease
4. Heart failure
5. Coronary artery disease
6. Cancer
7. Chronic liver disease
8. Cystic fibrosis

- Are a smoker
- Are exposed to certain chemicals or pollutants such as those used for agriculture, construction, or industrial chemicals. Exposure to these pollutants can sometimes cause damage to the lungs and contribute to lung inflammation—thus leaving the lungs more susceptible to infection.
- Suffer from alcoholism and have a weakened immune system

Symptoms

CAP sometimes presents after a cold, the flu, or any condition that damages the defenses of the airways that would allow bacteria to infect them. The symptoms of CAP can vary and generally overlap with other symptoms of the common cold or flu. This variability makes it sometimes difficult to recognize pneumonia. Many people attribute it to a cold that just won't go away. However, CAP can be life-threatening if it is not properly treated.

``Some symptoms that you may notice with community acquired pneumonia include, but are not limited to:

- Shaking and chills ,Fever
- A cough that produces sputum—usually rust colored (or burnt orange)
- Shortness of breath and Chest pain worsened by deep breathing or coughing and Night sweats

Treatment

Treatment for CAP varies according to the organism responsible for the infection. If the cause is bacterial, then the goal of treatment is to cure the infection with antibiotics, which can typically be taken orally at home if the infection is not severe. If the infection is severe, if the person is having difficulty breathing, or has other chronic medical conditions, then intravenous (IV—injected into a vein) antibiotics may be needed and are usually administered in a hospital. If the infection is viral, the goal is to alleviate any signs and symptoms of the infection through supportive care (such as fever reduction with acetaminophen) since there is no cure for a virus.

Because several treatment guidelines are available, the specific drug(s) that your doctor may use to treat your CAP may vary. Clinical expertise/preference and antibiotic drug resistance in a particular area are two factors that may affect a doctor's drug of choice for treating CAP.

At the initial visit to the doctor, he or she will question you about your past medical history and perform a physical examination. It may be necessary to perform a chest X-ray. Next, your doctor will determine how much your infection places your life at risk. Your doctor may need to send samples of your sputum, blood or urine to the laboratory to confirm your CAP diagnosis. Doctors will usually prescribe "empiric therapy"—prescribing therapy based on the suspected cause (bacteria, virus, or fungi) using clinical or practical expertise—because the specific organism responsible for the infection is usually not yet identified before treatment is started. After the organism is identified, therapy can be tailored to treat that specific organism. The following chart describes the guidelines from the Infectious Diseases Society of America and American Thoracic Society for patients that don't need to be hospitalized.

1.7 (ii) Toxoplasmosis

Definition

Toxoplasmosis is an infectious disease caused by the one-celled protozoan parasite *Toxoplasma gondii*. Although most individuals do not experience any symptoms, the disease can be very serious, and even fatal, in individuals with weakened immune systems.

Description

Toxoplasmosis is caused by a one-celled protozoan parasite known as *Toxoplasma gondii*. Cats, the primary carriers of the organism, become infected by eating rodents and birds infected with the organism. Once ingested, the organism reproduces in the intestines of cats, producing millions of eggs known as oocysts, which are excreted in cat feces daily for approximately two weeks. In the United States, it is estimated that approximately 30% of cats have been infected by *T. gondii*. Oocysts are not capable of producing infection until approximately 24 hours after being excreted, but they remain infective in water or moist soil for approximately one year. When cattle, sheep, or other livestock forage through areas with contaminated cat feces, these animals become carriers of the disease. Fruits and vegetables can also become contaminated when irrigated with untreated water that has been contaminated with cat feces. In humans and other animals, the organisms produce thick-walled, dormant structures called cysts in the muscle and other tissues of the body.

Most humans contract toxoplasmosis by eating cyst-contaminated raw or undercooked meat, vegetables, or milk products. Humans can also become infected when they come into contact with the *T. gondii* eggs while cleaning a cat's litterbox, gardening, or playing in a sand-box, for instance. Once infected, an individual is immune to reinfection. The incubation period or period between infection and the start of the disease ranges from several days to months.

Anyone can be infected by *T. gondii*, but usually only those individuals with weakened immune systems (immunocompromised) develop symptoms of the disease. For them, toxoplasmosis can be severe, debilitating, and fatal.

Immunocompromised individuals at risk include those with AIDS, cancer, or other chronic illnesses.

There is no person-to-person transmission, except from an infected mother to her child in the womb. Approximately six out of 1,000 women contract toxoplasmosis during pregnancy. Nearly half of these maternal infections are passed on to the fetus. Known as congenital toxoplasmosis, this form of the disease is acquired at birth by approximately 3,300 infants in the United States every year. The risk of fetal infection is estimated to be between one in 1,000 to one in 10,000. In children born with toxoplasmosis, symptoms may be severe and quickly fatal, or may not appear until several months or even years after birth.

Causes and symptoms

Healthy individuals do not usually display symptoms. When symptoms do occur, they are usually mild, resembling infectious mononucleosis, and include the following:

- Enlarged lymph nodes
- Muscle pains
- Fever that comes and goes
- General sick feeling

1.8 (iii) Trachoma

Definition

Trachoma is an eye infection caused by *Chlamydia trachomatis***,** which may result in chronic scarring and blindness if left untreated.

Alternative Names

Granular conjunctivitis; Egyptian ophthalmia

Causes, incidence, and risk factors

Trachoma is caused by infection with the bacteria *Chlamydiatrachomatis*. It has an incubation period of 5 to 12 days and begins slowly as conjunctivitis (irritation near the eye, "pink eye"), which if untreated may become chronic and lead to scarring.

If the eyelids are severely irritated, the eyelashes may turn in and rub against the cornea. This can cause eye ulcers, further scarring, visual loss, and even blindness.

Trachoma occurs worldwide -- primarily in rural settings in developing countries. It frequently affects children, although the consequences of scarring may not be evident until later in life. While trachoma is rare in the United States, certain populations marked by poverty, crowded living conditions, and/or poor hygiene are at higher risk for this illness.

Trachoma is acquired via direct contact with eye or nose-throat secretions from affected individuals or by contact with inanimate objects that are contaminated with these secretions, such as towels or clothes. In addition, certain flies that have fed on these secretions can transmit trachoma.

Symptoms

- Conjunctivitis
- Discharge from the eye
- Swollen eyelids
- Turned-in eyelashes
- Swelling of lymph nodes just in front of the ears
- Cloudy cornea

Signs and tests

Trachoma is definitely diagnosed by detection of the organism or antigen in conjunctival scrapings or by isolation of the bacteria in culture.

Treatment

Systemic therapy with oral antibiotics can prevent long-term complications if used early in the infection. Active antibiotics include erythromycin and its derivatives, or doxycycline. In certain cases, eyelid surgery for lid deformities may be needed to prevent chronic scarring which can lead to blindness if not corrected

Expectations (prognosis)

Early treatment before the development of scarring and lid deformities has an excellent prognosis.

Complications

- Scarring of the conjunctiva and cornea
- Lid deformities
- Turned-in eyelashes
- Visual loss -- if severe, may result in blindness

Calling your health care provider

Call your health care provider if you or your child recently visited an area of the world where trachoma is common and there are symptoms of conjunctivitis.

Prevention

Trachoma is spread by direct contact with eye, nose, and throat secretions from affected individuals or by contact with objects that may have been in contact with these secretions.

Improved sanitation and not sharing toilet articles such as towels are important measures for limiting the spread/acquisition of trachoma.

1.9. (iv) Mycobacterium Avium Complex (MAC)

Definition

MAC, formerly known as MAI, stands for Mycobacterium Avium Complex. MAC is a group of mycobacteria (the two most common being M. avium and M. intracellulare), that cause a serious disease in people with advanced AIDS. MAC most often causes a disseminated illness (bacteria is spread though the blood stream) and can cause many symptoms throughout the body.

MAC bacteria are found in air, water, soil, foods, some tobacco products, and in many animals. It is impossible to avoid contact with MAC bacteria. A recent study showed that person-to-person transmission of MAC bacteria is unlikely.

Risk factor

Risk factors for developing MAC include having fewer than 50 CD4 cells, a high viral load (greater than 90,000 copies per/ml), and having had another opportunistic infection such as CMV (cytomegalovirus).

Before HAART (Highly Active Antiretroviral Therapy), also known as the "cocktail," the number of people with AIDS who developed MAC reached as high as 40 percent. Since HAART, the number of people getting MAC has greatly declined.

Signs and symptoms

MAC can infect a person's entire body. The signs and symptoms of MAC can be the same signs of other diseases. They include high fever, drenching sweats, diarrhea, weight loss, abdominal pain, fatigue, weakness, anemia (low levels of red blood cells), neutropenia (low levels of white blood cells) or thrombocytopenia (low levels of platelets), and elevated liver function tests. The liver or spleen may be enlarged. Blood infections, hepatitis, skin lesions, and pneumonia may also occur.

Treatment

A doctor will usually give you a blood test to see if you have MAC. Although the blood test is the best test at this time, sometimes other tests are needed. Other tests may include stool samples and biopsies of the liver, digestive tract (gut), bone marrow, or other organs. Biopsies involve taking a sample of an organ using a big needle. Biopsies can be painful but are more reliable than stool samples.

Prevention

Yes, there are medications available that can help reduce one's risk of developing MAC. Preventive medication, also called prophylaxis, is recommended for anyone who is HIV-positive and has 50 CD4 cells or less. While rifabutin, clarithromycin, and azithromycin are all approved drugs for prophylaxis of MAC, clarithromycin and azithromycin are the preferred choices. You should talk with your doctor to see which one of these medications is best for you.

Treatment

Treatment for MAC involves taking a combination of antibiotics. MAC treatment must include at least two drugs, one of which should be either clarithromycin or Azithromycin. Ethambutol is the recommended second drug. Rifabutin, ciprofloxacin, or amikacin may be added for people with more severe

MAC. All of the drugs are pills except amikacin, which is given intravenously (IV).

In cases where people with MAC either do not respond to treatment at all or relapse after first responding to treatment, many doctors recommend a type of drug test that checks to see if the medications will work on the type of MAC a person has. This is called a drug susceptibility test. Susceptible means that the drugs will likely work, while resistant means that the drugs probably will not work. Susceptibility testing is recommended mainly for clarithromycin, azithromycin, and rifabutin, though other drugs might be tested as well.

MAC and the drugs used for treatment are hard on the body. You might consider visiting a nutritionist when you are first diagnosed with MAC so you can keep your weight up and prevent wasting. There are also medications available to help ease common MAC symptoms such pain, nausea, vomiting, and diarrhea, so do not be shy in asking for them.

1.10 Introduction of product Development

Product development usually begins when the active chemical entity has been shown to process the necessary attributes for a commercial product. Generally product development activities can be sub divided into formulation development and process development.

1.10.1 Formulation Development[1]

Formulation development provides the basic information on the active chemical, the formula and the impact of raw materials or excipients on the product. A typical supportive data generated during these activities may include:

1. Preformulation profile, which includes all the basic physical or chemical information about the chemical entity.
2. Formulation profile, which consist of physical and chemical characteristics required for the product, drug excipients compatibility studies, and effect of formulation on in-vitro dissolution.
3. Effect of formulation variable on the bioavailability of the product.
4. Specific test methods.
5. Key product attributes and specification
6. Optimum formulation

Formulation development should not be considered complete until all those factors which could significantly alter the formulation have been studied. Subsequent minor changes to the formulation, however, may be acceptable, provide they are thoroughly tested and as shown to have no adverse effect on product characteristics. In case of drug development process, compound tested is only one. A variety of studies must be performed for this single drug, each designed to characterize its efficacy, safety, selectivity or purity. Much of the data generation is driven by strict and extensive regulatory control and in this most of the studies are interdependent.

Objective: - The overall objective of a drug development process is to move product candidate through development so that a new drug applicant (NDA) or product license application (PLA) can be submitted as quickly as possible with best chance of approval.

1.10.2 Pharmaceutical issues in drug development

A) Role of excipients in drug development: - The bulk of final product in dosage form such as tablet, capsule etc the speed of disintegration, rate of dissolution/ release of drug, protection against moisture and stability during storage, as well as compatibility are determined by the excipients. Various excipients used are adhesives, absorbent excipients, liquid excipients, diluents, fillers, disintegrates, etc.

► The general characteristics of excipients are: -

- Must not react with drug substance.
- No effect on function of other excipients.
- Not interfere with the bioavailability of active material nor influence dissolution of the product.
- No pharmaceutical or physiological activity.
- Have consistent and stable chemical and physical characteristics & properties from batch to batch and ideally between suppliers.
- Colorless and not support microbiological growth in the product.

Performance characteristics of the excipient are

- Functionality: The control of functionality is important because many excipients have multiple functions or sometimes there is lack of awareness in some situations that excipients behave differently.
- Rework ability: The reworking potential is defined as the ratio of areas under the tensile strength compression profiles for re compression and for initial compression. Often the results show that recompression reduces tablet strength and that this reduction is more significant when the initial compaction is carried out at high pressure.
- Response and force loading rate:
- Modes of deformation: Tableting machines, which deform plastically with little elastic recovery, should produce better quality tablets than more resilient materials.
- Effects on compression rate: Mostly strength of the tablets depend on the speed of rotary tablet press and hence on rate of tablet compression. In virtually all the cases, increase in tablet press speed led to a decrease in tablet strength.

B) Dosage form design

A rational approach to dosage form design for any drug requires a complete understanding of its physiochemical and biopharmaceutical properties which can have a tremendous impact on its bioavailability and thereby on its efficacy and toxicity profile. Properties that dictate the selection and formulation of dosage forms include:

- Solubility and dissolution rate.
- Partition coefficient.
- Stability and/or degradation in physiologic fluids.
- Susceptibility to metabolic inactivation.
- Transport mechanism across biological membranes.

C) In vitro correlation

In vitro dissolution tests seem to be the most sensitive and reliable predictors of in vivo availability. Invitro in vivo correlations are classified as pharmacological correlations, semi quantitative correlations and quantitative correlations.

Drug development also includes phase 1, 2 and 3 trials carried out on a particular group of people after analogue development and screening process.

2.10.3 Process Development

Process development activities begin after the formulation has been developed. The process development should meet the following objectives:

1.Develop a suitable process to produce a product which meets all:

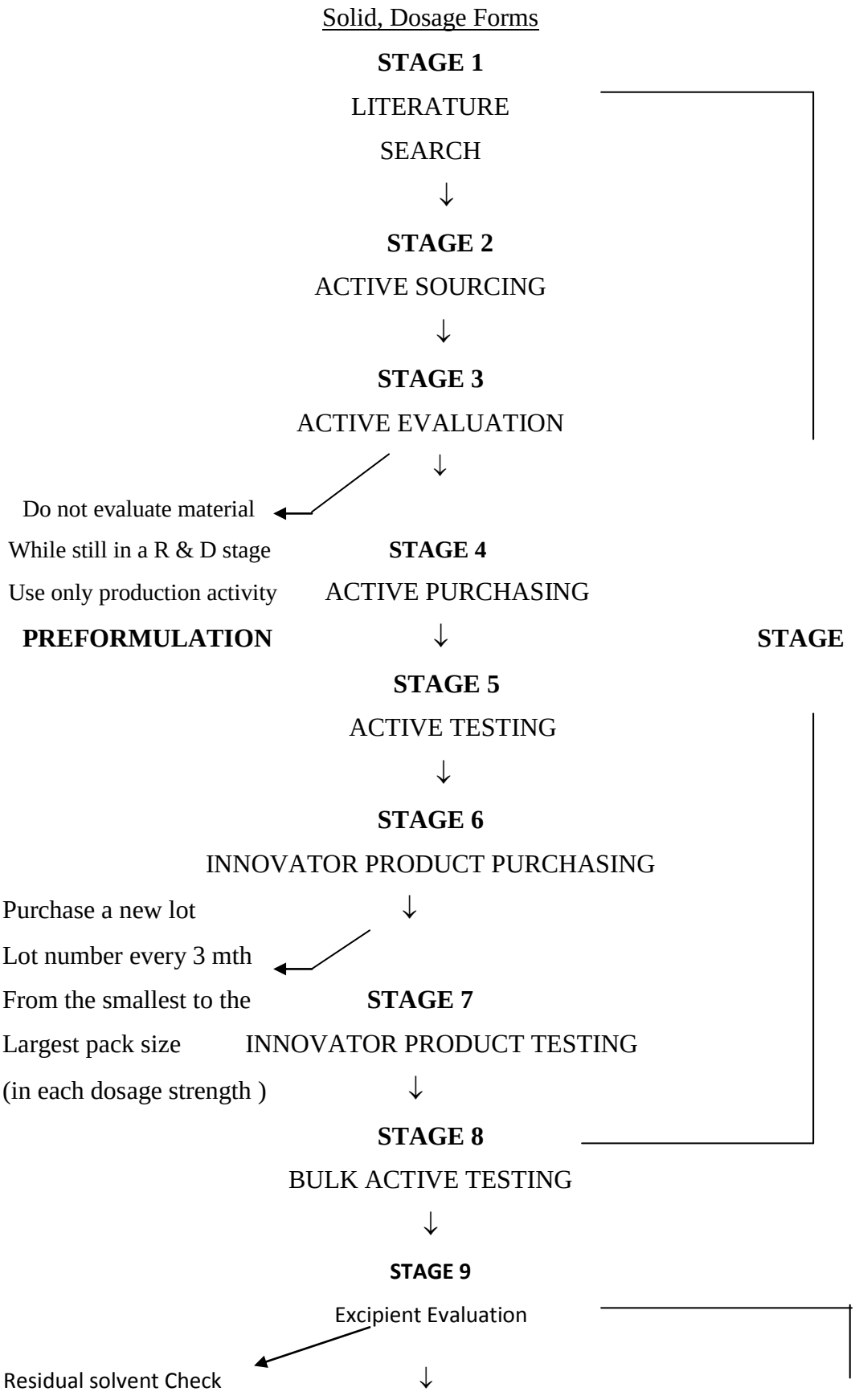
a. Product specifications
b. Economic constrains
c. cGMP

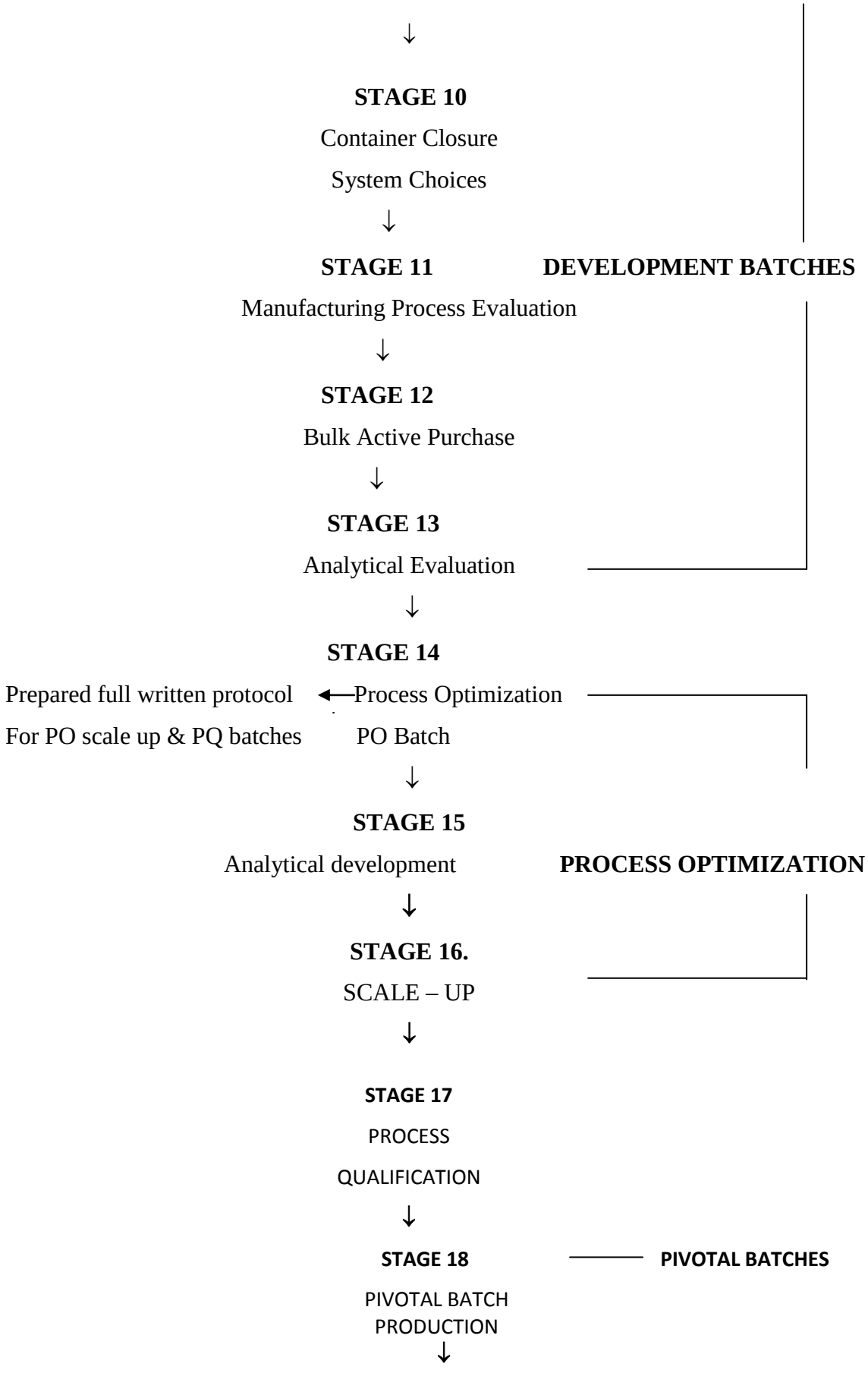
2.Identify the key process parameters that affect the product attributes

3.Identify in-process specification and test method

4.Identify generic and specific equipment that may required.

PRODUCT DEVELOPMENT FLOWCHART

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STAGE 10
Container Closure
System Choices
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STAGE 11
DEVELOPMENT BATCHES
Manufacturing Process Evaluation
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STAGE 12
Bulk Active Purchase
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STAGE 13
Analytical Evaluation
↓
STAGE 14
Prepared full written protocol
Process Optimization
For PO scale up & PQ batches
PO Batch
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STAGE 15
Analytical development
PROCESS OPTIMIZATION
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STAGE 16.
SCALE – UP
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STAGE 17
PROCESS
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STAGE 18
PIVOTAL BATCHES
PIVOTAL BATCH
PRODUCTION
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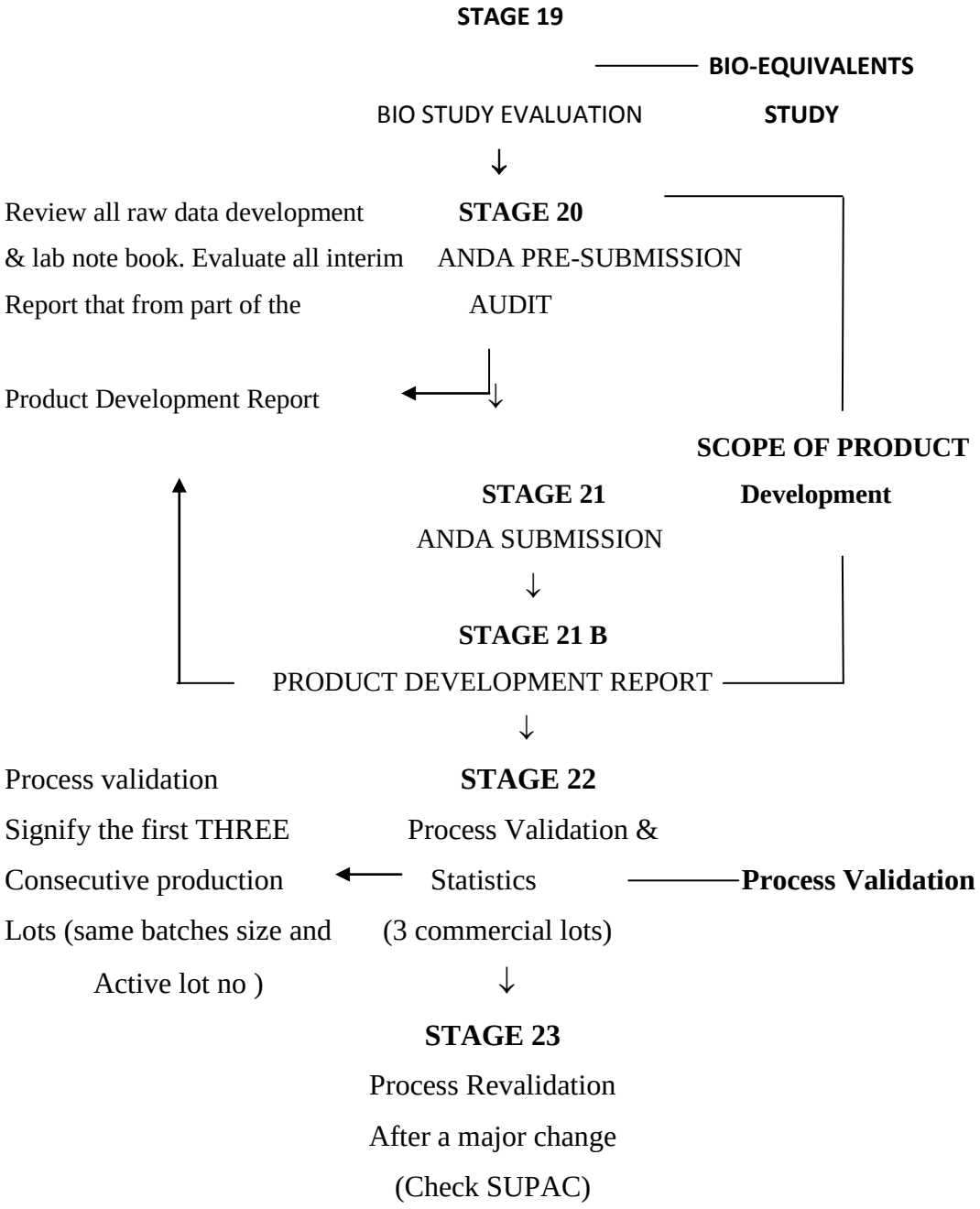

STAGE 19
BIO-EQUIVALENTS
BIO STUDY EVALUATION
STUDY
Review all raw data development
& lab note book. Evaluate all interim
Report that from part of the
Product Development Report
STAGE 20
ANDA PRE-SUBMISSION
AUDIT
SCOPE OF PRODUCT
Development
STAGE 21
ANDA SUBMISSION
STAGE 21 B
PRODUCT DEVELOPMENT REPORT
Process validation
Signify the first THREE
Consecutive production
Lots (same batches size and
Active lot no)
STAGE 22
Process Validation &
Statistics
(3 commercial lots)
Process Validation
STAGE 23
Process Revalidation
After a major change
(Check SUPAC)

1.11. Process development can be divided into several stages

a) **Design**
b) **Ranging**
c) **Characterization**
d) **Verification**

a) Design

This is the initial planning stage of process development. During this stage, technical operation in both the manufacturing and quality-control departments should be consulted. The practically and the reality of the manufacturing operation should be kept in perspective.

Key documents for the technical definition of the process are the flow diagram, the cause and effect diagram and the influence matrix.

The flow diagram provides a convenient basic on which to develop a detailed list of variables and responses. Preliminary working documents are critical, but they should never be "cast in stone", since new experimental data may drastically alter them. The final version will eventually be an essential part of the process characterization and technical transfer documents. Regardless of the stage of formulation/process development being considered, a detail identification of variables and response is necessary for early program planning.

As the development program progresses, new discoveries will provide an update of the variable and responses. It is important that current knowledge be adequately summarized for the particular process being considered. It should be pointed out, however that common sense and experience must be used in evaluating the variable during process design and development.

An early transfer of the preliminary documentation to the manufacturing and quality control department is essential, so that they can being to prepare for any new equipment or facilities that may required.

b) Ranging

Process-ranging studies will test whether identified parameter are critical to the product and process being developed. These studies determined the:

a. Feasibility of the design process
b. Criticality of the parameter
c. Failure limits for each of the critical variable
d. Validity of the test methods

This is usually a transition stage between the laboratory and the projected final process.

c) Characterization

Process characterization provides a systematic examination of critical variables found during process ranging. The objectives of these studies are:

a) Confirm key process control variables and quality their effect on product attributes.
b) Establish product conditions for each unit operation.
c) Determine in process operating limits to guarantee acceptable finished product and yield.
d) A carefully planned and coordinate experimental program is essential in order to achieve this objective.

d) Verification

Prior to a process being scale-up and transferred to production, verification is required. This ensures that it behave as designed under simulated production conditions and Determines its reproducibility. Key elements of the process-verification runs should be evaluated using well-designed in-process sampling procedure. These should be focused on potentially critical unit operations. Validated in-process and final product analytical procedures should always be used. Sufficient replicate batches should be produced to determine between and within-batch variations.

The typical process verification analysis of a tableted product include

Table NO: 2.1

Unit Operation	Analysis
Pre-blending	Blend uniformity, Dry-mix, Water content by KF apparatus
Granulation	None required
Sizing	Granules size distribution, Milled Granules-Water content by KF apparatus.
Blending	Blend uniformity, Flow properties
	Potency/assay
Tableting	Average weight
	Hardness
	Thickness
	Disintegration
	Dissolution
	Friability

The transfer procedure that is followed in order to pass the documented knowledge and experience gained during development and commercialization to an appropriate, responsible and authorized party. Technology transfer embodies both the transfer of documented and demonstrated technology, to the satisfaction of all parties and any and all applicable regulatory bodies.

1.12 Technology transfer subdivided into two units[6]:

- **Sending unit**
- **Receiving unit**

● **Advantages:**

- ✓ The transfer of technology from R & D (sending unit) to manufacturing (Receiving unit) is the first key steps to getting a high quality product to the market place.
- ✓ The transfers of the process technology from the R & D bench to large scale manufacturing present some unique challenges.
- ✓ It also useful to make a timeframe of the process for that particular product.
- ✓ Hold time studies is useful for the planning of the product with other batches.

● **Objectives:**

- ✓ To describe the appropriate information set that needs to be complied to support the transfer of the information and provide regulatory filing documents.
- ✓ To provide guidance on effective approaches for ensuring this information is available at "print of use" where guidance on specific topic already exists this will be referred.
- ✓ The technology transfer guide is planning in such a way that technology transfer performed in accordance with the recommendations in this guide will be the regulatory authorities.

1.12.1 Process Optimization[5]:

In the environment of increasing international competition where counters with lower production cost luckily catch up technologically, new thinking is required in order to meeting the competition is to focus on maximizing the utilization of exiting technology. This means much more than just investing in new equipment.

The ability to optimize or improve a process is dependent upon the ability to control the process. The ability to control the process is dependent upon the access to reliable and valid management.

The ability to control the processor. The ability to optimize the process is depend upon the access to reliable and valid managements. A successful industrial organization thus entails a strategic approach encompassing the whole chain.

A) Need for Optimization

In an environment of increasing competition where countries with lower production cost, quickly catch up technologically, new thinking is required in order to meet the competition. Efficient organization and leadership is more difficult to copy than technology. A successful way of meeting the increasing competition can thus be to focus the effort on adapting the organization for maximal utilization of existing technology and faster than competitors, being able to continuously introduce and make use of new technology.

B) Optimization Technology

There are two type optimization problems. They are:

1. Constrained Optimization:

Constrains are those restricted placed on the system due to physical limitation.

(Ex: Economic consideration)

2. Unconstrained Optimization:

In unconstrained optimization problems there are no restriction (such as tablet hardness and disintegration).

An additional complication in pharmacy is that formulations are not usually simple system. They often contain many ingredients and variables, which may interact with one another to produce unexpected.

1.12.3 Scale Up & Technology Transfer Consideration[7]

- Scale up means increase the batch size; it acts a link between the formulation research development and production.

  The pilot plant and its staff play a critical role in technology evolution scale-up and transfer activity of new products.

  • These activities being early in the development cycle and include technical aspects of process development and scale-up, organization and responsibility of technology transfer team, documentation of transfer process, and obtain preparation for an FDA pre-approval inspection. A properly design and operated pilot plant enhance the collection of scientific data necessary to support internal transfer activities as well as regulatory submission and FDA pre-approval inspection.

- Four key technical aspects must be addressed during scale-up in the pilot plant.

  Identification and control of critical component and formulation variables early in the development.

  Pilot plant equipment that simulates as closely as possible equipment used at The manufacturing site.

  Identification of critical process parameter and operating ranges with pilot plant equipment through the use of engineering and regret ion models.

  Collection of product and process data to adequately characterized each unit operation.

  The success of any program is highly dependant on the effectiveness of the communication presiding its implementation. Therefore, the preparation and distribution of a complete document summarizing the raw material and equipment requirements, manufacturing and packing process, process validation protocol, QC processor, safe handling processor as well as a detail plan of action out limiting expected result and time framer must be distributes prior to scale-up experiences.

- The three main considerations to be address during an effective technology transfer of plan. The person involved and process steps. Once prepared, the plan must be communicated to the involved part in research, at the corporate level and at the production site.

- The facility design plan a critical role in addressing each of their technical aspects, however scientific and pilot plant staff involved in manufacturing operations with in the pilot facility also play a key role in ensuring smooth and timely transfer of process technology to the manufacturing site.
- In the part, the transfer of formulation and, manufacturing technology was some times discretely processed from development staff with little interaction. Today, however, it is commonly recognize the interaction of these groups at an early development stage is critical in obtaining an efficient and successful transfer.
- Scientific and pilot plants staff a key role in demonstrating new product manufacturing techniques to produce personal in the pilot plant environment.
- A team orientation approach to the manufacture of pilot or large scale batches in the pilot plant will allow key production site personnel to view and comment on the process and make a specific recommendation for improvement based on the knowledge of the manufacturing site.

1.12.4 Introduction of Immediate Release Dosage Form:

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs.[8] Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules.[9, 10] The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluent and superdisintegrant.

The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of all drugs used to produce systemic effect are administered orally.[11] Rapidly disintegrating tablets have received much attention in recent years, as they are preferred by pediatric and geriatric patients. Moreover, the drug dissolution is facilitated by the tablets quick disintegration.

Bioavailability of a drug depends in absorption of the drug, which is affected by solubility of the drug in gastrointestinal fluid and permeability of the drug across gastrointestinal membrane. The drugs solubility mainly depends on physical – chemical characteristics of the drug. However, the rate of drug dissolution is greatly influenced by disintegration of the tablet.

The drug will dissolve at a slower rate from a nondisintegrating tablet due to exposure of limited surface area to the fluid. The disintegration test is an official test and hence a batch of tablet must meet the stated requirements of disintegration.

Disintegrants, an important excipient of the tablet formulation, are always added to tablet to induce breakup of tablet when it comes in contact with aqueous fluid and this process of desegregation of constituent particles before the drug dissolution occurs, is known as disintegration process and excipients which induce this process are known as disintegrants.

The objectives behind addition of disintegrants are to increase surface area of the tablet fragments and to overcome cohesive forces that keep particles together in a tablet.

1.13. Mechanism of tablet Disintegrant [12]

The tablet breaks to primary particles by one or more of the mechanisms listed below:-

1) By capillary action
2) By swelling
3) Because of heat of wetting
4) Due to disintegrating particle/particle repulsive forces
5) Due to deformation
6) Due to release of gases
7) By enzymatic action

1) By capillary action

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilic of the drug /excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

2) By swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

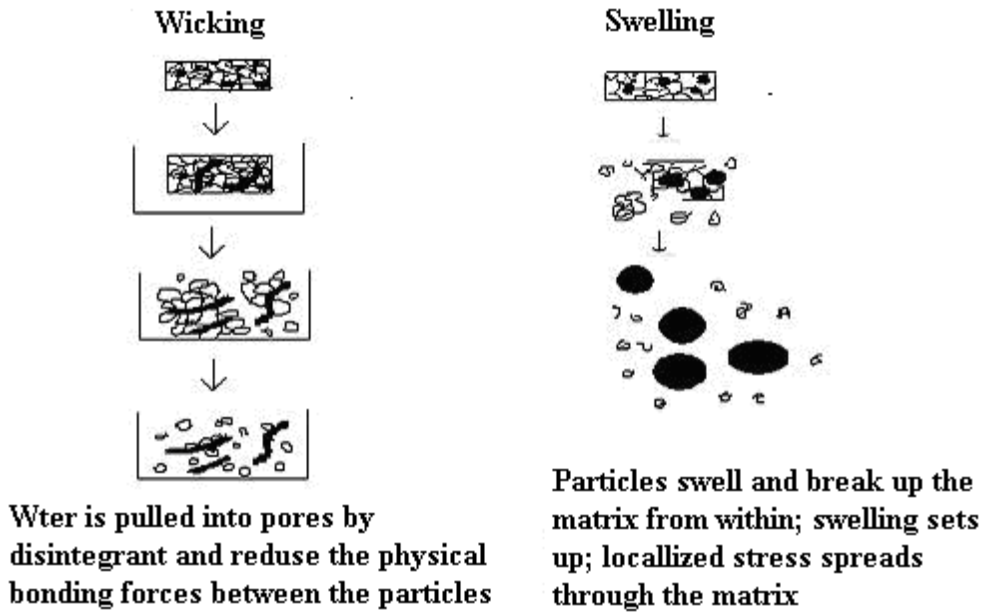


Figure.1 disintegration of tablet by wicking and swelling

3) Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

4) Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that no swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

5) Due to deformation.

Hess had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a break up of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

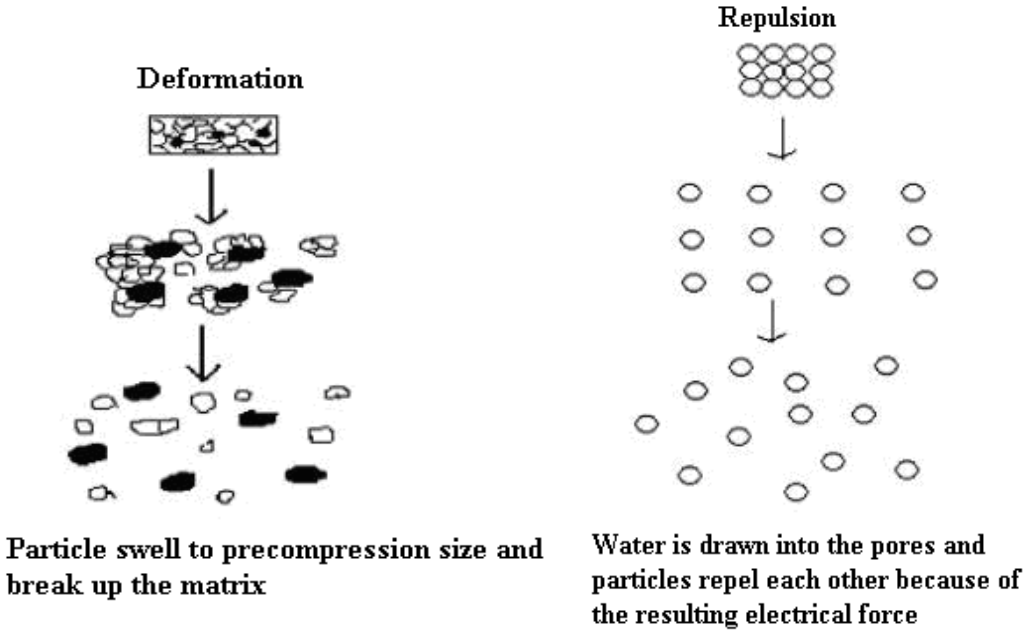


Figure.2. disintegration by deformation and repulsion:

6) Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

7) By enzymatic reaction

Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

Table.2.2.1. Disintegrating enzymes

Enzymes	Binder
Amylase	Starch
Protease	Gelatin
Cellulose	Cellulose and its derivatives
Invertase	Sucrose

Methods of addition of Disintegrants

The method of addition of disintegrants is also a crucial part. Disintegrating agent can be added either prior to granulation (intragranular) or prior to compression (after granulation i.e. extragranular) or at the both processing steps. Extragranular fraction of disintegrant (usually, 50% of total disintegrant requires) facilitates breakup of tablets to granules and the intragranular addition of disintegrants produces further erosion of the granules to fine particles.

1.13.1 Types of Disintegrants

1) Starch

Starch was the first disintegrating agent widely used in tablet manufacturing. Before 1906 potato starch and corn starch were used as disintegrants in tablet formulation. However, native starches have certain limitations and have been replaced by certain modified starches with specialized characteristics.

The mechanism of action of starch is wicking and restoration of deformed starch particles on contact with aqueous fluid and in doing so release of certain amount of stress which is responsible for disruption of hydrogen bonding formed during compression.

Lowenthal & Wood proved that the rupture of the surface of a tablet employing starch as disintegrant occurs where starch agglomerates were found. The conditions best suited for rapid tablet disintegration are sufficient number of starch agglomerates, low compressive pressure and the presence of water.

The concentration of starch used is also very crucial part. If it is below the optimum concentration then there are insufficient channels for capillary action and if it is above optimum concentration then it will be difficult to compress the tablet.

2) Pregelatinized starch

Pregelatinized starch is produced by the hydrolyzing and rupturing of the starch grain. It is a directly compressible disintegrants and its optimum concentration is 5-10%. The main mechanism of action of Pregelatinized starch is through swelling.

3) Modified starch

To have a high swelling properties and faster disintegration, starch is modified by carboxy methylation followed by cross linking, which is available in market as cross linked starch. One of them is sodium starch glycolate. Even low and®substituted carboxymethyl starches are also marketed as Explotab Primojel®.

Mechanism of action of this modified starches are rapid and extensive swelling with minimum gelling. And its optimum concentration is 4-6 %. If it goes beyond its limit,

then it produces viscous and gelatinous mass which increases the disintegration time by resisting the breakup of tablet. They are highly efficient at low concentration because of their greater swelling capacity.

Table.2.2.2 List of disintegrants

Disintegrations	Concentration in granules (%w/w)	Special comments
Starch USP	5-20	Higher amount is required, poorly compressible
Direct compression	5-15	--
Avicel®(PH 101, PH 102)	10-20	Lubricant properties and directly compressible
Solka floc®	5-15	Purified wood cellulose
Alginic acid	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Explotab®	2-8	Sodium starch glycolate, superdisintegrant
Polyplasdone®(XL)	0.5-5	Crosslinked PVP
Amberlite® (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC, HPMC	5-10	--
AC-Di-Sol®	1-3	Direct compression

4) Cellulose and its derivatives

Sodium carboxy methylcellulose (NaCMC and CARMELLOSE sodium) has highly hydrophilic structure and is soluble in water. But when it is modified by internally crosslinking we get modified crosslinked cellulose i.e. Crosscarmellose sodium which is nearly water insoluble due to cross linking. It rapidly swells to 4-8 times its original volume when it comes in contact with water.

5) Microcrystalline cellulose (MCC)

MCC exhibit very good disintegrating properties because MCC is insoluble and act by wicking action. The moisture breaks the hydrogen bonding between adjacent bundles of MCC. It also serves as an excellent binder and has a tendency to develop static charges in the presence of excessive moisture content. Therefore, sometimes it causes separation in granulation. This can be partially overcome by drying the cellulose to remove the moisture.

6) Alginates

Alginates are hydrophilic colloidal substances which has high sorption capacity. Chemically, they are alginic acid and salts of alginic acid. Alginic acid is insoluble in water, slightly acidic in reaction. Hence, it should be used in only acidic or neutral

granulation. Unlike starch and MCC, alginates do not retard flow and can be successfully used with ascorbic acid, multivitamin formulations and acid salts of organic bases.

7) Ion-exchange resin

Ion exchange resin (Ambrelite®IPR-88) has highest water uptake capacity than other disintegrating agents like starch and Sodium CMC. It has tendency to adsorb certain drugs.

8) Miscellaneous

This miscellaneous category includes disintegrants like surfactants, gas producing disintegrants and hydrous aluminium silicate. gas producing disintegrating agents is used in soluble tablet, dispersible tablet and effervescent tablet.

Polyplasdone®XL and Polyplasdone®XL10 act by wicking, swelling and possibly some deformation recovery. Polyplasdone®XL do not reduce tablet hardness, provide rapid disintegration and improved dissolution. Polyplasdone® as disintegrating agent has small

Particle size distributions that impart a smooth mouth feel to dissolve quickly. Chewable tablet does not require addition of disintegrant.

9) Superdisintegrants

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly. But have one drawback that it is hygroscopic therefore not used with moisture sensitive drugs.

And this superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

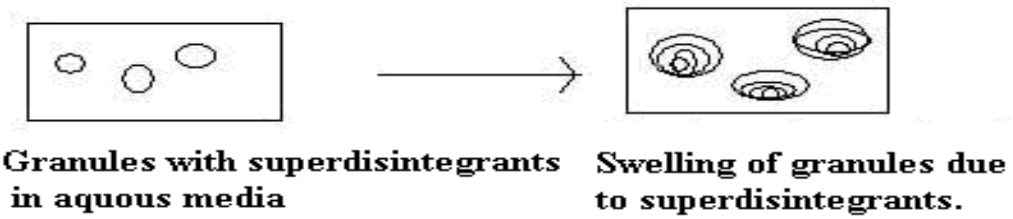


Figure.2.2.3 mechanism of superdisintegrants by swelling

1.14 Factors affecting disintegration

1) Effect of fillers

The solubility and compression characteristics of fillers affect both rate and mechanism of disintegration of tablet. If soluble fillers are used then it may cause increase in viscosity of the penetrating fluid which tends to reduce effectiveness of strongly swelling disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate. Insoluble diluents produce rapid disintegration with adequate amount of disintegrants. Chebli and cartilier proved that tablets made with spray dried lactose (water soluble filler) disintegrate more slowly due to its amorphous character and has no solid planes on which the disintegrating forces can be exerted than the tablet made with crystalline lactose monohydrate.

2) Effect of binder

As binding capacity of the binder increases, disintegrating time of tablet increases and this counteracts the rapid disintegration. Even the concentration of the binder can also affect the disintegration time of tablet.

3) Effect of lubricants

Mostly lubricants are hydrophobic and they are usually used in smaller size than any other ingredient in the tablet formulation. When the mixture is mixed, lubricant particles may adhere to the surface of the other particles. This hydrophobic coating inhibits the wetting and consequently tablet disintegration.

Lubricant has a strong negative effect on the water uptake if tablet contains no disintegrants or even high concentration of slightly swelling disintegrants. On the contrary, the disintegration time is hardly affected if there is some strongly swelling disintegrants are present in the tablet. But there is one exception like sodium starch glycolate whose effect remains unaffected in the presence of hydrophobic lubricant unlike other disintegrants.

4) Effect of surfactant

Table.2.2.3 the effects of various surfactants

Surfactant	Remarks
Sodium lauryl sulfate	Good-various drugs Poor - various drugs
Polysorbate 20	Good
Polysorbate 40 & 60	Poor
Polysorbate 80	Good
Tweens	Poor
Poly ethylene glycol	Poor

(Good – decrease in disintegration time, Poor – increase in disintegration time)

Sodium lauryl Sulphate increased absorption of water by starch or had a variable effect on water penetration in tablets. Surfactants are only effective within certain concentration ranges. Surfactants are recommended to decrease the hydrophobicity of the drugs because the more hydrophobic the tablet the greater the disintegration time. Aoki and fukuda claimed that disintegration time of granules of water-soluble drugs did not seem to be greatly improved by the addition of nonionic surfactant during granulation , but the desired effect of a surfactant appeared when granule were made of slightly soluble drugs.

1.15 Antibacterial agent[42]

Definition: These are agents which are used for the to kill or inhibit the bacteria.

1.15.1Classification of antibacterial agent:

The antibacterial agents are classified according to its mode of action.

(A) Antibacterial agents which interfere with the synthesis or action of folate.

1. Sulphonamide
2. Trimethoprim

(B) Beta-lactam antibiotics

1. Penicillin
2. Cephalosporins and Cephamycin
3. Other β – lactam antibiotics

(C) Antibacterial agents affecting bacterial protein synthesis.

1. Tetracyclines
2. Chloramphenicol
3. Aminoglycosides
4. Macrolides
   - i. **Azithomycin**
   - ii. Erythromycin
   - iii. Clarithomycin

(D) Antibacterial agents affecting topoisomerase-2

1. Fluoroquinolones

(E) Miscellaneous antibacterial agents

1. Glocopeptide
2. Polymixin antibiotics
3. Bacitracin
4. Metronidazole
5. Nitrofurantion

(F) Antimycobacterial agents for treat to tuberculosis.

1. Streptomycin
2. Isoniazide
3. Rifampicin
4. Ethambutal
5. Pyrazinamide
6. Capreomycin
7. Cycloserine

(G) Antimycobacterial agents for treat to leprosy

1. Dapsone
2. Rifampicin
3. Cloazimine

1.15.2 Macrolides antibiotics

The macrolides are a large group of antibacterial mainly derived from Streptomycess spp.and having a common macrocyclic lactone ring to which one or more sugar is attached. They are all weak base and only slightly soluble in water .Their properties are very similar and in general they have low toxicity and a similar spectrum of antimicrobial activity with cross-resistance b/w individual members of the group. The macrolides are bacteriostatic or bactericidal depending on the concentration and the type of micro-organism and are thought to interfere with bacterial protein synthesis. Their antimicrobial spectrum is similar to that of benzyl penicillin but they are also active against such organisum as legionella pneumophila, mycoplasm pneumoniae and some rickettsias, chlamydias and chlamydophilas.

Macrolides and related drug have a postantibiotic effect; that is antibacterial activity persists after concentration have dropped below the minimum inhibitory concentration.

1.15.3 Biochemical reaction as potential target

Class -1 reaction:

Class-1 reaction are not promising targets, for two reason.

1st – there is no very marked difference b/w bacteria and human cells in the mechanism for obtaining energy from glucose since both use the embden-meyerh of pathway and the citric acid cycle.

2nd – even if the glucose pathways were to be blocked a large verity of other compounds (amino acids lactate etc).

Class-2 reaction

Class-2 reactions are better targets since some pathways involved in class-3 reaction exust in parasitic but not in human cells. For instance human cells have in the course of evolution lost the ability possessed by bacteria to synthesis lost the ability passed by bacteria to synthesis some amino acids the so called essential amino acids and also the growth factors or vitamins any such difference represents apotential target. Another type of target occur when a pathways is identical in both bacteria and man but has differential sensitivity to drug.

Class-3 reaction

Class-3 reaction are particularly good targets for selective toxicity because every cell has to make its own macromolecules. These cannot be picked up from the environment and there are very distinct differences b/w mammalian cells in the pathways involved in class-3 reaction. In the class-3 reaction protein are synthesized.

1.15.4 Protein synthesis

The ribosome are cytoplasmic nucleoprotein structures that are the basic units of machinery for the synthesis of protein on messenger RNA templates. They are different in eukaryotes and prokaryotes and this provides the basis for the selective antimicrobial action of some antibiotics. The bacterial ribosome consists of a 50s subunit and a 30s subunit. In this respect it differs from the mammalian ribosome which has a 60s and 40s subunit. A simplified version of protein synthesis in bacteria is as follows. Messenger RNA which is transcribed from DNA becomes attached to the 30s subunit of the ribosome which moves along the mRNA so that successive condones of the messenger pass along the ribosome from the right the "A" position to the left the "P" position as show in ,The "P" site contains the graving peptide chain attached to a molecule of transfer RNA.The next amino acid residue to be added linked to its specific tRNA with its distinctive anticodon-moves into the A site being bound to the site by a codan,anticodon recognition, which occur by complementary base-pairing. A transpeptidation reaction occurs which links the incoming tRNA at the 'A' site. The tRNA from which the peptide chain has removed is now ejected from the "P" site. The tRNA at the A site is Tran located to the P site and the ribosome moves on one codon relative to the messenger. A new tRNA with amino acid attached and with the relevant anticodon now moves into the "A" site and the whole process is repeated.

CHAPTER - 2

AZITHROMYCIN DRUG PROFILE

2.1 DRUG-PROFILE [13, 14, 15, 16, 17 & 18]

Azithromycin is a newer macrolide that was developed to overcome some of the shortcoming of erythromycin such as intolerance, pharmacokinetics, and limited antimicrobial pectrum.Azithromycin (technically an **azalide**) has a **15-membered** ring, which is derived from the insertion of an **amino group** into the erythromycin ring.Azithromycin has unique pharmacokinetics that give rise to prolonged tissue levels, which allow briefer duration of therapy(3to5 days) for most infections and a single-dose regimen of treatment of chlamydial STDs.It contain two molecules of water.

Chemical abstracts registry no

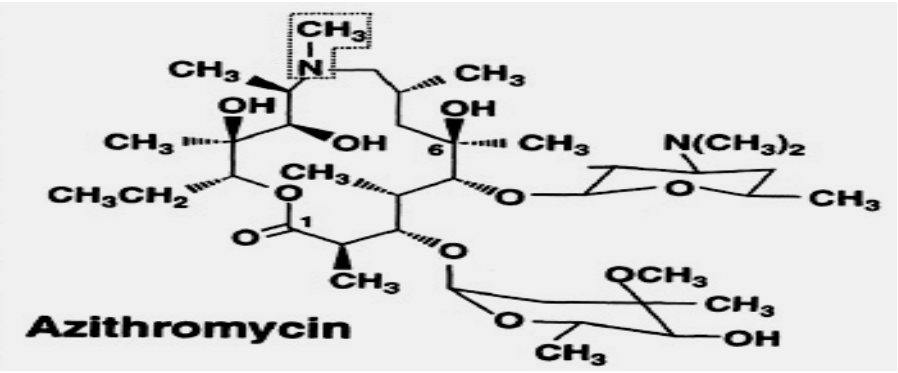
(i) For anhydrous- [83905-01-5]

(ii) For dehydrate- 117772-70-0

Chemical abstracts name:

(2R, 3S, 4R, 5R, 8R, 10R, 11R, 12S, 13S, 14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one

Structure:



2.1.1 Physical and chemical properties

Mol. Formula Anhydrous Dihydrate	 $C_{38}H_{72}N_2O_{12}$ $C_{38}H_{72}N_2O_{12}.\ 2H_2O$
Mol. Wt Anhydrous Dihydrate	 748.98 785.0
% Composition	C- 60.94% H- 9.69% N-3.74% O- 25.63%
State	solid (crystalline power)
Odor	Odorless
Taste	not available
M.P	113- 115 ºC (for anhydrous) 126 ºC (for dihydrate)
Color	white
pH	9.0 to 11.0
Solubility	Practically insoluble in water, freely soluble in anhydrous ethanol and in methylene chloride.
Specific optical rotation	-45 to -49 (anhydrous substance)
Water contain	1.8% to 6.5% determined on 0.200g
Sulphate ash	maximum 0.2%, determined on 1.0gm
Heavy metals	maximum 25 ppm

Azithromycin Tablet:-

Azithromycin Tablet contain not less than 90.0% and not more than 110.0% of the labeled amount of Azithromycin

Description:

White tablet or film coated tablets with White or almost white coar.

Identification

Dissolve quantity of the powder tablets in ethanol to produce a solution of 10mg of Azithromycin/ml and filter, using successive filtrate as a test solution. Dissolve a quantity of Azithromycin LRS in ethanol to produce a reference solution of 10mg of Azithromycin/ml, the solution comply with test (1) for identification describe under Azithromycin.

Dissolution:

Carryout the dissolution test (method-2) using a phosphate BS (to 6000ml of 0.1mol/L disodium hydrogen phosphate solution add 40ml of hydrochloric acid, adjust the ph value to 6.0) 900ml as the dissolution medium ,adjust the rotation speed of the paddle to 100 rpm.Withdraw the solution after exact 45 minute and filter. Dilute an accurately measured quantity of the successive filtrate with the same solvent to produce a solution of 55µg per ml ,as test solution .Triturate 10 tablets to an accurately weight quantity equivalent to about the average wt of one tab add aquantity of ethanol(using 1ml of ethanol for 2mg of the labeled amount of Azithromycin) and the dissolution medium, shake for 30 minutes or ultrasonic ate for 10 minutes to dissolve Azithromycin.Dilute an accurately measured quantity of the successive filtrate with the dissolution medium to produce a solution of 55µg per ml and filter, using the successive filtrate as the reference solution. Measure accurately 5ml each of the two solution separately to two tubes with stoppers respectively and accurately 5ml of sulfuric acid solution (75→100) mix well, allow to stand for 30 minutes ,cool measure the absorbance of the resulting solution at 482nm.Calculate the dissolution of Azithromycin form each tablet not less than 75% is dissolve.

Assay:

Weigh accurately and triturates 10 tablets dissolve accurately weighed quantity equivalent to 0.25gm Azithromycin in 125ml of ethanol, dilute with sterile water to produce a solution of 1000unit per ml, mix well, carry out the assy describe under Azithromycin using the supernatant liquid.

Storage:

Preserve in tightly closed container stored in dry place.

References:

1) Pharmacopoeia of people's republic of china Vol-II ,(2005)

2. 2 Pharmacokinetics

Absorption

Azithromycin given orally is about 40% bioavailability absorption from capsule, but not tablet is reduced by food. Peak plasma concentration are achieved 2-3 hours after a dose but Azithromycin extensively distributed to the tissue and tissue concentration subsequently remain much higher than these in the blend. In contrast to other antibacterial plasma concentration is therefore, a little value as a guide to efficacy. High concentrations are taken of in to add blood cell. Azithromycin is more stable than erythromycin at gastric ph. The Pharmacokinetic profile of Azithromycin reflects a rapid and extensive uptake from the circulation into intracellular compartment, followed by slow release. Azithromycin has been show to penetrate tissues rapidly and extensively,steady-state levels were 0.64µg/ml at 2 to 4hr,0.1µg/ml at 10 to 12hr,and 0.012µg/ml at 72 to 96hr.Azithromycin remains in human polymorph nuclear leukocytes in vitro for several hr even after extra cellular drug has been removed ,and its release can be stimulated by phagocytosis. Azithromycin level in pulmonary macrophages, polymorphonuclear leukocyte, tonsillar tissue and genital or pelvic tissue remain increased for extended periods, with a mean tissue half –life of 2to 4 days.

Distribution

Azithromycin is distributes widely throughout the body, except to the brain and CSF. Azithromycin has unique pharmacokinetic properties include extensive tissue distribution and high drug concentration within cells(including phagocytes)resulting in much greater concentration of drug in tissue or secretion compared to simultaneous serum concentration. Tissue fibroblast acts as the natural reservoir for the drug in vivo. Protein binding is 50% at very low plasma concentration and less at higher concentration..

Metabolism and Excretion

A small amount of Azithromycin are demethylated in the liver and it is excreted in bile as unchanged drug and metabolites. About 6.0% of oral dose(representing about 20% of the amount in the systemic circulation) is excreted in urine. The terminal elimination half life 40 to 68hr is prolonged because of extensive tissue sequestration and dinding.

2. 2.1 Resistance:

Resistance to macrolides usually results from one of four mechanisms

(i) Drug efflux by an active pump mechanism (en coded by mrsA, mefA, or mefE in staphylococci,group A. streptococci ,or S.pneumoniae, respectively.

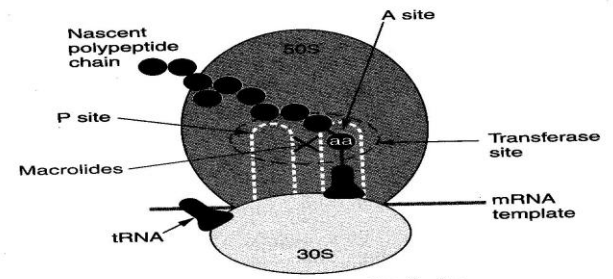
(ii) Ribosomal protection by inducible or constitutive production of methylase enzyme, mediated by expression of ermA,ermB AND ermC, which modify the ribosomal target and decrease drug binding.

(iii) Macrolides hydrolysis by esterases produced by enterobacteriaceae.

(iv) Chromosomal mutation that alter a 50s ribosomal protein (found in B.sub ilis, complyobacter spp, mycobacteria and gram-positive cocci.

2.3 Mode of action

Macrolide antibiotics are bacteriostatic agents that inhibit protein synthesis by binding reversibly to the 50s ribosomal subunit of sensitive organisum.Azithromycin appears to inhibit the translocation step where in the nascent peptide chain temporarily residing at the a site of the transferase reaction fails to move to the P or donar site alternatively macrolides may bind and cause a conformational change that terminates proteins synthesis by indirectly interfering with transpeptidation and translocation. Fig no.1



Inhibition of bacterial protein synthesis by the macrolide antibiotics azithromycin.

Fig no- 1

2.4 Side Effects

Minor: Abdominal pain, diarrhea, dizziness, headache, nausea, or vomiting.

These effects should disappear as your body adjusts to Azithromycin.

Azithromycin can cause increased sensitivity to sunlight. It is important to avoid prolonged exposure to sunlight and sunlamps. Wear protective clothing, and use an effective sunscreen.

If you feel dizzy or light-headed, sit or lie down for a while; get up slowly from a sitting or reclining position; and be careful on stairs.

Major, palpitations, rash, rectal or vaginal itching, shortness of breath, swelling of the face or neck, sore throat, unusual bruising or bleeding, or yellowing of the eyes or skin. If your symptoms of infection seem to be getting worse rather than improving, you should contact your doctor.

2.5 Drug- Interactions

Azithromycin interacts with several medications:

- Azithromycin may increase blood levels of aminophylline, theophylline, carbamazepine, cyclosporine, tacrolimus, disopyramide, phenytoin, digoxin, triazolam, phenobarbital, ergotamine, dihydroergotamine, or oral anticoagulants (blood thinners, such as warfarin) when they are used concurrently; this may lead to serious side effects.
- Antacids containing aluminum or magnesium will decrease the efficacy of Azithromycin. Take antacids one hour before or two hours after your dose of Azithromycin.
- Do not take Azithromycin if you are taking pimozide; increased adverse effects on the heart may result.

Adverse reactions

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting,

diarrhea, or abdominal pain. Rarely but potentially serious side effects were angioedema and cholestatic jaundice

Storage :

to store this medicine:

- Keep out of the reach of children.
- Store away from heat and direct light.
- Store the pediatric suspension form of azithromycin in the refrigerator.
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children

CHAPTER - 3

3.1 AIM AND OBJECTIVE

To develop formulation of pharmaceutical equivalent of formulation and product development of azithromycin tablets.

Selection criteria of immediate release dosage form

1.) longer half life
2.) Poor solubility
3.) To need the immediate action of the drug.
4.) Absorption from mainly stomach.
5.) Long elimination half life

Azithromycin:

- Azithromycin is Anti-bacterial agents. It is used for mainly MAC infection, community acquired pneumonia and trachoma disorders. Very low solubility in aqueous media & oral bioavailability is 37%.its half life is 68 hrs & clearance is 630 ml/min.
- As per literature it is observed that Azithromycin the newest generation of macrolides is as effective and better tolerated, and associated with a lower risk of adverse effects.
- It is more stable in the gastric **pH**.
- Azithromycin prevents bacteria from growing by interfering with their ability to make protein.
- The macrolides antibiotics do not interfere with humans' ability to make protein.
- Azithromycin is effective against a wide variety of bacterial organisms.
- Azithromycin has the advantage of shorter treatment regimens and improved tolerance.
- For better bioavailability drug should release fast from formulation to media. This can be performing with a disintegrant agent.

- Physical properties show that poor flow properties so we can conclude about the key ingredients of our formulation to make a fast release tablet.

In the development of Azithromycin tablet we using, Microcrystalline cellulose, Croscarmellose sodium, Pregelatinized starch, Sodium lauryl Sulphate, Syloid 244 FP, Magnesium Stearate, Hypromelose, PEG-6000, Titanium di oxide. Pre-formulation testing is the first step in rational development of dosage form of drug substance, in this study characterization of drug API is most important study, solubility study, practical size analysis of API, Bulk density, Tapped density, and compressibility of the API was done. For development of Azithromycin formulation known about the details of innovator product. To develop a non – infringing formulation of Azithromycin, which is stable and bio-equivalent to Zithromax of Pfizer. We select the dissolution media as per the U.S.P, phosphate buffer pH 6.0 with tripsin in 900 ml at 100 rpm, NLT 75 % dissolved in 45 minutes. Accelerated stability testing was done as per the ICH guidelines and successful formulation was found highly stable in all respects.

Keeping above factor in view it is aimed to develop formulation of pharmaceutical equivalent Azithromycin as an immediate release dosage form.

CHAPTER - 4

LITERATURE REVIEW

KM Olsen et al **(2005)**[19] Intrapulmonary pharmacokinetics of Azithromycin in healthy volunteers given five oral doses. The intrapulmonary pharmacokinetics of oral Azithromycin were studied in 25 healthy volunteers, each of whom received an initial dose of 500 mg and then 250 mg once daily for four additional doses. Bronchoscopy, bronchoalveolar lavage, and venipuncture were performed 4, 28, 76, 124, 172, 244, 340, and 508 h after the first dose was administered. Azithromycin concentrations in epithelial lining fluid (ELF), alveolar macrophages, peripheral blood monocytes, and serum were measured by high-performance liquid chromatography. Azithromycin was extensively concentrated in cells and ELF. Drug concentrations in AMs (peak mean +/- standard deviation, 464 +/- 65 micrograms/ml) exceeded 80 micrograms/ml up to 508 h (21 days) following the first dose, while concentrations in PBMs (peak, 124 +/- 28 micrograms/ml) exceeded 20 micrograms/ml up to 340 h (14 days). Azithromycin concentrations in ELF peaked at 124 h (3.12 +/- 0.93 micrograms/ml) and were detectable up to 172 h (7 days), when they were 20 times the concurrent serum concentrations. Although the clinical significance of antibiotic concentrations in these compartments is nuclear, the sustained lung tissue penetration and extensive phagocytic accumulation demonstrated in this study support the proven efficacy of azithromycin administered on a 5-day dosage schedule in the treatment of extra cellular or intracellular pulmonary infections.

R Mason ET AL (2012)[20] Spectrum and mode of action of Azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms The macrolide antibiotic azithromycin (CP-62,993; 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A; also designated XZ-450 [Pliva Pharmaceuticals, Zagreb, Yugoslavia]) showed a significant improvement in potency against gram-negative organisms compared with erythromycin while retaining the classic erythromycin spectrum. It was up to four times more potent than erythromycin against Haemophilus influenzae and Neisseria gonorrhoeae and twofold more potent against Branhamella catarrhalis, Campylobacter species, and Legionella species. It had activity similar to that of erythromycin against Chlamydia spp. Azithromycin was significantly more potent versus many genera of the family Enterobacteriaceae; its MIC for 90% of strains of Escherichia, Salmonella, Shigella, and Yersinia was less than or equal to 4 micrograms/ml, compared with 16 to 128 micrograms/ml for erythromycin.

Azithromycin inhibited the majority of gram-positive organisms at less than or equal to 1 micrograms/ml. It displayed cross-resistance to erythromycin-resistant Staphylococcus and Streptococcus isolates. It had moderate activity against Bacteroides fragilis and was comparable to erythromycin against other anaerobic species. Azithromycin also demonstrated improved bactericidal activity in comparison with erythromycin. The mechanism of action of azithromycin was similar to that of erythromycin since azithromycin competed effectively for [14C] erythromycin ribosome binding sites.

Suhagia BN ET AL [21]Determination of Azithromycin in pharmaceutical dosage forms by spectrophotometric methodA simple and sensitive spectrophotometric method has been developed for determination of Azithromycin in its pharmaceutical dosage forms. In the proposed method, azithromycin is oxidized with potassium permanganate to liberate formaldehyde, which is determined in situ using acetyl acetone, in the presence of ammonium acetate. A yellow coloured chromogen was obtained, having absorption maxima at 412 nanometer. The method is found to be linear in the concentration range of 10-75 microgram per milliliter, with regression coefficient of 0.9978. Various parameters such as concentration of potassium permanganate and reagent, time required for oxidation, and maximum colour intensity were optimized. The method was validated, and can be used successfully to assay azithromycin in its pharmaceutical dosage forms viz. tablets, capsules and injections.

Hooda AK ETAL [22]Azithromycin in the treatment of gingival hyperplasia in renal allograft recipients of cyclosporineBackground: Gingival hyperplasia is a known complication of Cyclosporine therapy. We studied the efficacy of Azithromycin in the treatment of gum hyperplasia in renal transplant patients on follow-up in our center. Methods: All renal transplant recipients with symptomatic gum hyperplasia were given Azithromycin for a period of 5 days in a dose of 500 mg on day 1 followed by 250 mg OD on days 2-5. The ratio of crown height and width in each of the 8 incisors was measured before starting therapy, at 4 weeks and at 8 weeks after therapy. Results: There were 122 renal transplant recipients on our follow-up. Of these, 115 were on Cyclosporine. Out of these, 11 patients (Males 9, Females 2) had symptomatic gum hyperplasia (9.56 percent). The symptoms in patients with gum hyperplasia were pain and bleeding from the gums. The average duration on Cyclosporine therapy in these patients was 25.8 months (3 to 36 months). Symptomatic relief was seen in all patients after Azithromycin therapy. The average value of ratio of crown height and width increased from pre-treatment baseline of 1.06 plus 0.11 to 1.18 plus 0.11 (at 4 weeks)

and to 1.24 plus 0.09 at 8 weeks after therapy (p less than 0.001). The drug was well tolerated and none of the patients reported any side effects. There was no significant change in the creatinine level at 1 month after Azithromycin therapy. Cyclosporine C2 assays done in 3 patients before and 4 weeks after therapy also showed no significant change. Conclusion: We conclude that Azithromycin is a safe and effective therapy for Cyclosporine induced gum hyperplasia.

Singhi MK et all [23] Comparison of oral Azithromycin pulse with daily Doxycycline in the treatment of acne vulgarisIntroduction: Oral Azithromycin has been advocated by some in the treatment of acne. However, its efficacy has not been established. Material and Methods: This non-randomized controlled trial was conducted on 70 outpatients with acne vulgaris to compare the efficacy and safety of Azithromycin and doxycycline in the treatment of inflammatory acne. In the first group, azithromycin was administered 500 mg daily before meals for 3 consecutive days in a 10-day cycle, with the remaining seven days in each cycle being drug-free days. The second group was given doxycycline 100 mg daily after meals. Topical erythromycin was prescribed to all patients. Clinical assessment was done at 10-day intervals for both the groups up to three months. We followed the severity index described by Michaelsson for assessment of outcome measures. Results: There was 77.26 percent improvement in Aazithromycin treated group in comparison to 63.74 percent in the doxycycline treated group. There was a statistically significant reduction in severity in the azithromycin treated group. Conclusion: The study showed that a combination of Azithromycin with topical erythromycin was significantly better than doxycycline with topical erythromycin in the treatment of acne vulgaris. The incidence and severity of side effects were also lower with Aazithromycin.

Ogale SB et al [24] Comparative evaluation of the efficacy and safety of Azithromycin and Roxithromycin in children suffering from otitis media An open, randomized, comparative study was undertaken to compare the efficacy and safety of Azithromycin (Kid tablets) with Roxithromycin (Kid tablets) in the treatment of otitis media in children. 51 patients of either sex, under 12 years and presenting with signs and symptoms of otitis media were included in the study. The patients were randomly assigned to two groups and received either Azithromycin tablet 10 mg/kg once daily for 3 days or Roxithromycin tablet 2.5-5 mg/kg twice daily for 7 days. The daily mean severity scores measuring the ear discharge suggested that there was a statistically significant fall in the severity scores in the Azithromycin group from day 1 onwards, whereas of the other signs and symptoms showed a statistically significant fall from day

2 onwards in the Azithromycin group as compared to day 4 in the Roxithromycin group. Both Azithromycin and Roxithromycin were equally well tolerated by the children with only one incidence of rash in the Roxithromycin group. 77 percent of the patients in the Azithromycin group were assessed as being cured as compared to only 36 percent of patients in the Roxithromycin group. 23 percent of patients in the Azithromycin group had improved as compared to 64 percent of patients in the Roxithromycin groups. The advantages of Azithromycin in the treatment of otitis media include broad spectrum of activity, pharmacokinetic properties that allow once daily dosing and short course therapy. Azithromycin is an appropriate choice for the treatment of otitis media in children.

H. Rautelin1 et al [25]Azithromycin resistance in Campylobacter jejuni and Campylobacter coliAbstract The MICs of erythromycin, Azithromycin and ciprofloxacin were determined for 60 human fecal isolates of*Campylobacter*. Of these, 30 strains selected on the basis of their resistance to erythromycin by disk diffusion were highly resistant to both erythromycin and Azithromycin. Nine of these selected isolates were resistant to ciprofloxacin. The remaining 30 strains were non-selected, consecutive isolates of*Campylobacter* susceptible to erythromycin by disk diffusion and were shown to be two- to five-fold more susceptible to Azithromycin than to erythromycin as determined by MIC testing.

R. Haye1 et al [26] Azithromycin versus placebo in acute infectious rhinitis with clinical symptoms but without radiological signs of maxillary sinusitis Abstract In this double-blind, parallel-group, multicenter study, 169 patients with symptoms of maxillary sinusitis but without radiographically confirmed empyema (pus) were randomly assigned to receive either 500 mg Azithromycin once daily for 3 days (87 patients) or placebo daily for 3 days (82 patients). Nasal secretion, maxillary tenderness and pain, nasal obstruction, general malaise, and hyposmia were assessed at the start of the study and on days 4, 11, and 25 of treatment. After 11 days 58% of the patients in the Azithromycin group were cured versus 31% in the placebo group; after 25 days the cure rate was 79% versus 67%, respectively. When both cure and improvement were considered, the corresponding figures after day 25 were 90% and 88%, respectively. Adverse events, predominantly gastrointestinal, occurred in 24 (27%) of the Azithromycin-treated patients and in 15 (18%) of those treated with placebo, but the difference was not statistically significant. There was a difference in efficacy in favor of Azithromycin in the treatment of rhinitis with symptoms of maxillary sinusitis but

without radiological signs of empyema (pus). Antibiotics should only be used to alleviate symptoms in patients with moderate to severe symptoms, as the results after 25 days for both improvement and cure are equal. In the treatment of acute rhinitis with symptoms and signs of maxillary sinusitis but without empyema, treatment with Azithromycin seems to result in a better cure rate after 10–12 days when compared with placebo.

J Retsema, et al [27] Spectrum and mode of action of Azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms.The macrolide antibiotic Azithromycin (CP-62,993; 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A; also designated XZ-450 [Pliva Pharmaceuticals, Zagreb, Yugoslavia]) showed a significant improvement in potency against gram-negative organisms compared with erythromycin while retaining the classic erythromycin spectrum. It was up to four times more potent than erythromycin against Haemophilus influenzae and Neisseria gonorrhoeae and twofold more potent against Branhamella catarrhalis, Campylobacter species, and Legionella species. It had activity similar to that of erythromycin against Chlamydia spp. Azithromycin was significantly more potent versus many genera of the family Enterobacteriaceae; its MIC for 90% of strains of Escherichia, Salmonella, Shigella, and Yersinia was less than or equal to 4 micrograms/ml, compared with 16 to 128 micrograms/ml for erythromycin. Azithromycin inhibited the majority of gram-positive organisms at less than or equal to 1 micrograms/ml. It displayed cross-resistance to erythromycin-resistant Staphylococcus and Streptococcus isolates. It had moderate activity against Bactericides fragilis and was comparable to erythromycin against other anaerobic species. Azithromycin also demonstrated improved bactericidal activity in comparison with erythromycin. The mechanism of action of azithromycin was similar to that of erythromycin since Azithromycin competed effectively for [14C] erythromycin ribosome binding sites.

Sivasubramanian L et al [28] Visible spectrophotometric methods for the determination of Azithromycin in tabletsTwo visible spectrophotometric methods have been developed for the estimation of Azithromycin in pure and in pharmaceutical formulations. The first method (A), a visible spectrophotometric method was based on the formation of a red colored chromogen with ferric chloride and 1,10-phenanthroline, which showed absorbance maximum at 490 nm and Beer's law was obeyed in the concentration range of 2.5-15 micro-g/ml. The second method (B) was based on the formation of a blue colored chromogen with Folin-Ciocalteau reagent, which showed

maximum absorbance at 720 nm and Beer's law was obeyed in the concentration range of 25-150 micro-g/ml. Results of analysis for both the methods were validated statistically and by recovery studies. ottom of Form

3. 2 Review of work done of Immediate Release dosage form

Becker C, Dressman JB, et al [29] Biowaiver monographs for immediate release solid oral dosage forms: IsoniazideBecker C et al Literature data relevant to the decision to allow a waiver of in vivo bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing isoniazid as the only active pharmaceutical ingredient (API) are reviewed. Isoniazid's solubility and permeability characteristics according to the Biopharmaceutics Classification System (BCS), as well as its therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions and reported BE/bioavailability (BA) problems were taken into consideration. Isoniazid is "highly soluble" but data on its oral absorption and permeability are inconclusive, suggesting this API to be on the borderline of BCS Class I and III. For a number of excipients, an interaction with the permeability is extreme unlikely, but lactose and other deoxidizing saccharides can form condensation products with isoniazid, which may be less permeable than the free API. A biowaiver is recommended for IR solid oral drug products containing isoniazid as the sole API, provided that the test product meets the WHO requirements for "very rapidly dissolving" and contains only the excipients commonly used in isoniazid products, as listed in this article. Lactose and/or other deoxidizing saccharides containing formulations should be subjected to an in vivo BE study.

Dumont ML et al [30] Probability of passing dissolution acceptance criteria for an immediate release tablets Dumont ML et al During development of solid dosage products, a pharmaceutical manufacturer is typically required to propose dissolution acceptance criteria unless the product falls into Biopharmaceutics Classification System (BCS) class I, in which case a disintegration test may be used. At the time of filing the new drug application (NDA) or common technical document (CTD), the manufacturer has already met with regulatory agencies to discuss and refine dissolution strategy. The dissolution acceptance criteria are based on stability and batch history data and are often arrived at by considering the percentage of batches that pass United States Pharmacopeia (USP) criteria at Stage 1 (S(1)), when in fact, the product is deemed unacceptable only when a batch fails USP criteria at Stage 3 (S(3)) [H. Saranadasa, Disso. Technol. 7 (2000) 6-7, 18 [1]]. Calculating the probability of passing (or failing)

dissolution criteria at S(1), S(2), or S(3) can assist a manufacturer in determining appropriate acceptance criteria. This article discusses a general statistical method that was developed to assess the probability of passing the multistage USP test for dissolution and how it was applied to an immediate release tablet formulation. In this case, acceptance criteria were set and the analysis was conducted to assess the probabilities of passing or failing based on this acceptance criterion. Whether the acceptance criteria were relevant to the product was also considered. This mathematical approach uses a Monte Carlo simulation and considers a range of values for standard deviation and mean of historical data.

Qureshi SA et al [31] Applications of a new device (spindle) for improved characterization of drug release (dissolution) of pharmaceutical products Qureshi SA et al a crescent spindle (patent pending) is described which may be used in place of the USP paddle component in USP dissolution apparatus 2. The new spindle is curve shaped, corresponding to the bottom of a dissolution vessel, with attached bristles to fill in the gap between the spindle and the surface of the vessel. The geometry of the new spindle provides more efficient mixing than the USP paddle and prevents accumulation of disintegrated material (no cone formation). Using the new spindle, in comparison with the USP paddle, dissolution characteristics of three drug products: 250 mg amoxicillin capsules, 15.6 g acetylsalicylic acid (ASA) boluses and 200 mg carbamzepine tablets were evaluated. The experimental conditions for dissolution testing with the two stirring devices included; 900 ml of 0.05 M phosphate buffer, pH 6.8 with 50 rpm, 900 ml of 0.05 M acetate buffer, pH 4.5-ethanol (7:3) with 50 rpm, and water containing 1% sodium lauryl sulphate with 75 rpm for amoxicillin capsules, ASA boluses and carbamazepine tablets, respectively. Uncharacteristic of the test products, which are fast release, the USP paddle provides significantly slower drug release. For example, 90 min for <80% drug release vs. 10 min for >90% for amoxicillin capsules and 6 h for 80% vs. 30 min for >90% for ASA boluses with USP paddle vs. the new spindle. In case of the carbamazepine tablets, three products which are bioequivalent and prescribed interchangeably, the USP paddle method shows significantly different dissolution characteristics. However, with the new device, all these products show similar drug release characteristics, a better reflection of product release characteristics and in vivo drug release behaviour. Compared with the USP paddle, the suggested device (spindle) provides improved stirring and mixing which appears to provide more appropriate (biorelevant) characterization of pharmaceutical products.

Yu LX et al [32] we sought to evaluate whether U.S. Pharmacopeia (USP) apparatus 3 can be used as an alternative to USP apparatus 2 for dissolution testing of immediate-release (IR) dosage forms. Highly soluble drugs, metoprolol and ranitidine, and poorly soluble drugs, acyclovir and furosemide, were chosen as model drugs. The dissolution profiles of both innovator and generic IR products were determined using USP apparatus 2 at 50 rpm and apparatus 3 at 5, 15, and 25 dips per minute (dpm). The dissolution profiles from USP apparatus 3 were compared to those from USP apparatus 2 using the f(2) similarity test. The dissolution profile from USP apparatus 3 generally depends on the agitation rate, with a faster agitation rate producing a faster dissolution rate. It was found that USP apparatus 3 at the extreme low end of the possible agitation range, such as 5 dpm, gave hydrodynamic conditions equivalent to USP apparatus 2 at 50 rpm. With appropriate agitation rate, USP apparatus 3 can produce similar dissolution profiles to USP apparatus 2 or distinguish dissolution characteristics for the IR products of metoprolol, ranitidine, and acyclovir. Incomplete dissolution was observed for the furosemide tablets using USP apparatus 3. Although it is primarily designed for the release testing of extended-release products, USP apparatus 3 may be used for the dissolution testing of IR products of highly soluble drugs, such as metoprolol and ranitidine, and some IR products of poorly soluble drugs, such as acyclovir. USP apparatus 3 offers the advantages of avoiding cone formation and mimicking the changes in physiochemical conditions and mechanical forces experienced by products in the gastrointestinal tract.

Influence of higher rates of agitation on release patterns of immediate-release drug products

Shah VP et al [33] The dissolution procedure serves as a quality control test to assure batch-to-batch uniformity and bioequivalence of a product once the bioavailability of the product has been established. It can also be used to detect manufacturing and/or process variations that could reduce product bioavailability. Dissolution testing must be conducted at an appropriate agitation rate. Tests conducted at high agitation rates may lose the ability to differentiate between good and bad products. Although the effect of high agitation rates has been known for some time, several immediate-release drug products still have United States Pharmacopeia (USP) monograph dissolution procedures that require very high agitation rates. A systematic survey was conducted on marketed tablets of chloroquine phosphate, griseofulvin, hydroxychloroquine sulfate, isocarboxazide, primaquine phosphate, and sulfadiazine. Each of these products has a USP monograph requiring a dissolution test at a paddle speed of 100 rpm. To study the influence of agitation rate on the dissolution rate of these products, dissolution studies were conducted at paddle speeds of 50, 75, and 100 rpm with the USP apparatus 2 (paddle method). The dissolution rate increased with an increase in the agitation rate from 50 to 75 rpm. However, no significant increase in the dissolution rate was noted with an increase in the agitation rate from 75 to 100 rpm. The data support the position that the higher agitation rate of 100 rpm is not necessary for a quality control procedure or a compendia standard for the products tested.

3 Patent Survey:

(i) Drug substance

Patent no	Assignee/applicant	Clues from the invention
US6268489	Pfizer	Monohydrate Azithromycin is hygroscopic. It is most difficult to prepare and maintain this monohydrate in a from having a contant,reproducible water content. it is particularly difficult to handle during formulation ,since at higher RH levels, the monohydrates readily picks up varying amount of water. Such problems have been over come by the present invention of stable dihydrate.
US7056893	Insite vision	Azithromycin antibiotic have a maximum stability over a ph interval of about 5.0 to 7.0 preferably with at a ph of about 6.3
WO03/053399	Pfizer	Azithromycin can be produced in many different forms. For example, the current commercial from of Azithromycin is a stable, crystalline, non-hygroscopic dihydrate, also referred to as from A. The commercial tablet is then formulated by using water as the granulating liquid. Several crystalline non-dihydrate forms of Azithromycin are also known. From B is hygroscopic crystalline hydrate. This form of Azithromycin is difficult to handle during formulation due to its propensity for readily absorbing varying amount of water.
EP01127580	Pfizer	The bioavailability of Azithromycin can be increased by co-administering Azithromycin with a p- glycoprotein inhibitor.
WO03063838	Pfizer	Dry granulated formulations of Azithromycin (using non-dihydrate form of Azithromycin)
WO03053416	Pfizer	Directly compressible formulation of Azithromycin (using non dihydrate from of Azithromycin)
WO2004087096	Pliva	Pharmaceutical composition having reduced bitter taste.
EP00679400	Pfizer	The invention provides the use of Azithromycin in the manufacture of a rapidly disintegrating oral dosage form with high bioavailability for the treatment of a microbial infection in a mammal that has eaten or will eat in the period commencing 1 hour prior to dosing and terminating 2 hour after dosing.
WO2006115494	Abraxis	A stable, sterile liquid formulation comprising lyophilized Azithromycin, ethanol, citric acid &/or NaoH.

CHAPTER – 5

Formulation development

5.1 Objective:

To develop a non-infringing formulation of Azithromycin, which is stable and bioequivalent to Zithromax of Pfizer and being marketed in domestic.

The strength to be developed is 250 mg.

Qualitative composition of the formulation with respect to the Excipients would be same as that of the innovator.

Quantitative composition would be derived by trials, to ensure a drug product having similar physico-chemical properties as that of the innovator.

Manufacturing Process:

The same manufacturing process and the equipments used during development would be similar to the intended commercial scale equipments.

5.2 Selection of Excipients

Sourcing

The excipients used during development were procured from qualified vendors.

5.2.1 Function and Justification[41]

Diluents: In view of drug dose it is essential to add bulking agents or diluents to increase the weight of the tablet. Microcrystalline cellulose was selected as the main diluent.

Disintegrant: Cross carmellose sodium we selected as superdisintegrant. The strong correlation of disintegration time to bioavailability. Thus, it is important to optimize the disintegration time in order to enhance in vivo dissolution of the drug. In order to release the active ingredient from a solid dosage form matrix as efficiently as possible, disintegrate is often used in the formulation, especially

when the dosage forms are compressed with binder. Disintegrates help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form.

Binder: Pregelatinized starch was used as a tablet binder in the concentration of 0.5 – 5 %.Formulators skilled in art can determine the binder level for the formulations, but binder usage level of 2-25% in tablet formulations is common.

Lubricants: Magnesium Stearate is a widely used as Tablet and Capsule lubricant. It is generally used in the concentrations between 0.25 – 5.0 %.

Glidant: Colloidal Anhydrous Silica is widely used as Tablet and Capsule Glidant. It is generally used in the concentrations between 0.25 – 3.0 %.

Lubricants: Magnesium Stearate is a widely used in Tablet and Capsule as a lubricant. It is generally used in the concentrations between 0.25 – 5.0 %.

Film former: Hypromellose is widely used in oral and topical pharmaceutical formulation. It is generally used in coating suspension in the concentrations between 50- 30.0 %.

Coating agent: titanium dioxide is widely used in oral pharmaceutical formulations as white pigment and as opacifier in film coating. it is generally used in the concentrations b/w 10.0 – 30.0 %.

Plasticizer: polyethylene glycol 6000 is widely used as plasticizer in film coating of tablet. It is generally used in the concentrations b/w 5.0 – 20.0 %.

Granulation vehicle: Water is widely used for granulating Agent because of no any toxic effect and for non- aqueous solvent we widely use Isopropyl alcohol.

Wetting agent: Sodium lauryl sulfate is mainly used as wetting agent. It is generally used in the concentrations b/w 1.0 – 2.0 %.

5.3 Selection of Dissolution Medium

Initially dissolution was done with reference product Aazithral in phosphate buffer, pH 7.5 in 900 ml with type -2 apparatus at 100 rpm.

Later on, it was decided to comply with I.P draft monograph dissolution test

Dissolution media: sodium phosphate buffer pH 6.0 with trypsin

Apparatus: USP II (Paddle)

RPM: 100

Time points: 5, 10, 15, 20, 30, 45 minutes

Identification: HPLC

Limit: NLT 75 % labeled amount should release in 45 minutes

Table no- 6.1 comparative dissolution profile of Azithromycin 250 mg tablets in different batches.

Fig – no 2

Batch no	**Dissolution media**	**Time (min)**			
		10	**15**	**30**	**45**
250/015	Sodium phosphate buffer pH 6.0 with trypsin	59.2	73.7	82.6	95.2%
250/018	,,	57.3	74.4	81.7	97.2%
250/020	,,	58.5	75.7	82.9	98.1%

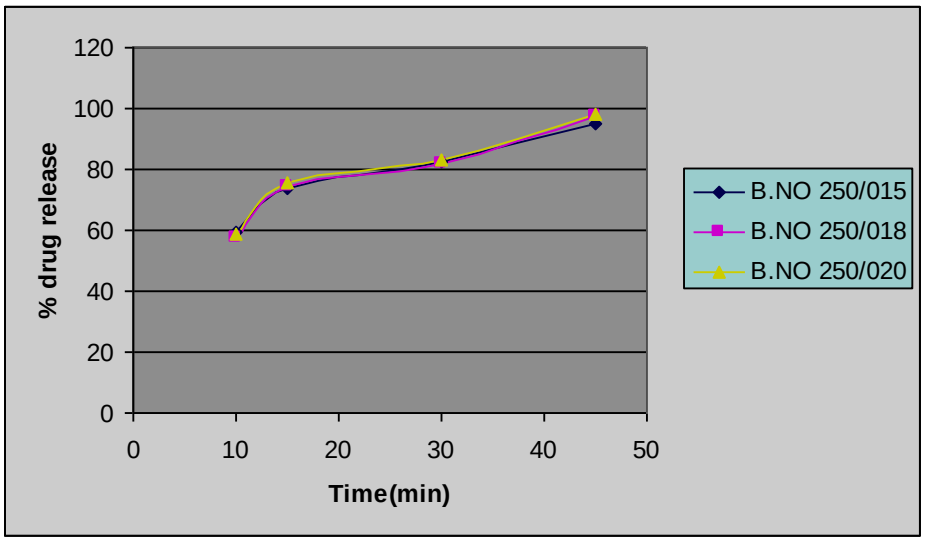


Fig –no 2: comparative dissolution profile of Azithromycin 250 mg tablets in different batches.

5.6 Development Trial

Trial no:-1 prototype formula

In the 1st trial we take the excipent as per the innovator**.**

IFF qualitative formulation

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Calcium phosphate dibasic	Dilunt
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Hypromelose	Film former
6	Lactose	Diluent
7	PEG-6000	Plasticizer
8	Titanium di oxide	Opacifier

Observation: Capping is occur

Remark: API is crystalline, milling required so API is milled by 0.3 mm screen and passed in 80 #.

Trial no:-2

In this trial API is milled through the 0.3 mm screen and passed through mesh # 80

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Calcium phosphate dibasic	Diluent
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Hypromelose	Film former
6	PEG-6000	Plasticizer
7	Titanium di oxide	Opacifier

Observation: Sticking is occurs

Remark: Replacement of Dibasic calcium Phosphate with Microcrystalline cellulose to improve compressibility

Trial no: - 3

In this trial we use microcrystalline cellulose as a diluent and to decrease the stickiness

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Microcrystalline cellulose	Diluent
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Hypromelose	Film former
6	PEG-6000	Plasticizer
7	Titanium di oxide	Opacifier

Observation: Again we found sticking

Remark: Add aerosol to reduce the stickiness

Trial no: -4

In this trial we used Aerosil to reduce the stickiness

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Microcrystalline cellulose	Diluent
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Aerosil	Glidant
6	Hypromelose	Film former
7	PEG-6000	Plasticizer
8	Titanium di oxide	Opacifier

Observation: Improve but DT increased & abrasiveness in blend

Remark: To solve this problem we Add Sodium lauryl Sulphate to improve wettability of API

Trial no: - 5

In this to solve the problem of stickiness we adding Sodium lauryl Sulphate

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Microcrystalline cellulose	Diluent
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Sodium lauryl Sulphate	Wetting agent
6	Aerosil	Glidant
7	Hypromelose	Film former
8	PEG-6000	Plasticizer
9	Titanium di oxide	Opacifier

Observation: Again slightly sticking occur but DT ok

Remark: To solve again this problem we adding of Syloid in place of Aerosil**.**

Trial no: - 6

In this trial we used Syloid in place of Aerosil.

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Microcrystalline cellulose	Diluent
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Sodium lauryl Sulphate	Wetting agent
6	Syloid	Glidant
7	Hypromelose	Film former
8	PEG-6000	Plasticizer
9	Titanium di oxide	Opacifier

Observation: Slightly sticking is occur but at later stage

Remark: We increased binder addition & kneading time and sizing with 1.2 mm in place of 1.00 mm

Trial no: - 7

In this trial we increased binder addition time kneading time and sizing through 1.2 mm screen

Sr.No	Ingredients	Function
1	Pregelatinized starch	Binder
2	Microcrystalline cellulose	Diluent
3	Croscarmellose sodium	Disintegration
4	Magnesium Stearate	Lubricants
5	Sodium lauryl Sulphate	Wetting agent
6	Syloid	Glidant
7	Hypromelose	Film former
8	PEG-6000	Plasticizer
9	Titanium di oxide	Opacifier

Observation: No sticking is occurring

Remark: Finalization of formulation

Componenents and composition of the final Formula

Strength: 250 mg

Sr.No	Ingredients	Function	Qty/tablet(mg)	% w/w
1	Azithromycin (as dehydrate)	Active	262.00*	81.88
2	Microcrystalline cellulose	Diluent	19.06	5.96
3	Croscarmellose sodium	Disintegrant	2.90	0.91
4	Pregelatinized starch	Binder	12.00	3.75
5	Sodium lauryl Sulphate	Wetting agent	0.64	0.20
6	Purified water	Granulating fluid	Qs	Qs
7	Syloid 244 FP	Glidant	4.80	1.81
8	Magnesium Stearate	Lubricant	4.80	1.50
9	Hypromelose	Film former	6.05	1.89
10	PEG-6000	Plasticizer	0.85	0.27
11	Titanium di oxide	Opacifier	0.50	0.16
12	Quinoline yellow	Colorant	0.10	0.03

* 785 mg Azithromycin dehydrate ~ 749 mg Azithromycin anhydrous.

6.0 PRODUCT OPTIMIZATION

Following parameter were studied with for the optimization of manufacturing process and check robustness of formula.

6.1 Dispensing:

Dispense the all the materials as per robust formula. All material dispense under control room temp.

6.2 Shifting:

Shift the material API through 80 # and other material through 40 # and 60 # There is no residue found on their surface.

6.3 Dry mixing:

Using rapid mixing granulator (capacity – 6 lit.) for dry mixing and granulation

Dry mixing time optimize with trial of mixing at different time interval.

Sample no.	3 min.	5 min.	8 min.
S-1	92.6	99.6	100.5
S-2	96.3	101.1	98.9
S-3	95.6	100.4	99.5
S-4	95.8	98.9	99.35
S-5	94.2	99.35	99.3
S-6	91.5	97.8	100.3
S-7	98.3	99.7	98.9
S-8	95.4	100.6	100.5
S-9	96.8	99.8	98.9
S-10	99.6	99.5	99.3
Avg.	95.61	99.68	99.55
SD	2.30	0.88	0.62
Composite assay (%)	96.5	100.2	99.4

Conclusion:

From the above result, 5 minutes BUA RSD is very less, so 5 to 8 minutes mixing is efficient during dry mixing. Dry mixing at 5 min. gives satisfactory result.

6.4 Granulation:

Optimization of binder addition time

Impeller slow				**Impeller fast**			
1-2 min.	2-3 min.	3-4 min.	5-7 min.	1 min.	2 min	3 min	5 min
Not good wetted and no granules forms	Not good wetted and no granules forms	Good granules are not found.	Uniform addition and good granule	Dusting problem during granulation. Granules become hard in nature.			

The dry mix powder is not bulky, so impeller slow is good for granulation. Binder addition with 5 to 7 minutes gives satisfactory result. Chopper will off during binder addition to prevent dusting of powder.

Conclusion:

Binder addition time was optimized as 5 to 7 mint with impeller slow and chopper off... This gives satisfactory result.

6.5 Kneading:

Kneading time – High kneading retard the dissolution due to hard granules formed.

Low kneading produce better result but it is unable to break the lumps and produce less uniformity of granulation process.

Kneading time	**High (5-6 mints)**	**Optimum(2-4 mints)**	**Low (1-3 mints)**
Dissolution time in minutes	% drug released		
5	35	45.8	60.8
10	42.6	56.5	65.8
15	48.6	60.5	70.4
20	55.9	65.3	75.3
30	75.5	78.9	80.5
45	82.5	88.4	88.5

Conclusion:

Kneading time was optimized as 2 to 4 mints with impeller fast and chopper fast.

6.6 Drying time

In granulation process the granulating agent is used purified water. So dry is required for remove the amount of water.

Set the temp as 60° C for 20 mints and drying up to us got the LOD becomes 3 to 4 %.

6.7 Sizing

screen size	**0.8 mm**	**1.0 mm**	**1.2 mm**
Granule characteristic	Passed particle are fine and high quantity of residue	Low residue quantity	Fine and coarse both particles, negligible residue

Conclusion:

Sizing through 1.2 mm screen produce optimum ratio of fine and coarse thus sizing through 1.2 mm screen gives satisfactory result.

6.8 Blending

Blending time is optimized with trial at different period of blending.

Sample no.	5 min.	8 min.	10 min.	12 min.
S-1	90.30	92.40	95.13	97.32
S-2	91.33	97.72	94.50	98.52
S-3	88.91	94.45	96.17	94.65
S-4	87.92	97.58	96.48	97.57
S-5	78.36	96.26	96.76	97.41
S-6	89.04	95.54	96.00	96.98
S-7	92.33	95.14	96.34	96.00
S-8	97.62	96.15	96.42	94.53
S-9	92.58	95.31	96.79	96.35
S-10	95.71	97.34	96.40	96.80
Avg	90.41	95.79	96.10	96.71
SD	5.22	1.69	0.76	0.80
Composite assay	94.80	97.00	95.62	96.05

Conclusion: 10 minutes gives low SD value and good assay result.

6.9 Lubrication:

Lubrication time is optimizing with trial at different period of mixing.

RPM was set as 10 to 20.

Sample no.	3 mints	5 mints	7mints
L – 1	95.2	99.2	98.6
L – 2	91.1	99.4	94.6
L – 3	95.5	97.5	97.5
L – 4	96.2	98.8	99.8
L – 5	98.7	100.2	99.4
L – 6	99.4	99.1	100.1
L – 7	94.3	98.3	99.7
L – 8	95.3	98.9	96.4
L – 9	98.3	99.7	99.2
L – 10	99.5	99.9	98.7
Avg	96.35	99.1	98.4
SD	2.52	0.75	1.66
Composite Assay	96.4	100.1	98.6

Conclusion: ok

6.10 Tablet compression:

Selection of punch and die

Compress the granules into tablets on rotary compression machine using 12/32" SC, Plain/Plain (D tooling) punches plain on both the sides.

Parameters set up:

1. Set up of tablet weight and marketing requirements we are selecting punch and die. This tablet weight is 312.00 mg ± 3 %.
2. Set up of hardness

Effect of hardness on friability:

Sample	Hardness range (N)	Friability	Dissolution (%) in 45 minutes
1	50 – 90	0.39	88.6
2	90 – 130	0.15	89.7
3	130 – 170	0.09	78.5

Conclusion:

We set various hardness 50 to 200 N

Product Composition:

6.11 Demo Batch:

6.11.1 Product Composition:

Strength: 250 mg

Lot A: Granulation

S. No.	Ingredients	Spec.	Function	%w/w	Qty Tab. (In mg)	Qty./ Batch (g)
	Dry mix:					
1	Azithromycin (as dihydrate)	USP	Active	81.88	262.00	1572.00[$]
2	Microcrystallin e cellulose	IP	Diluent	5.96	19.06	114.36[$]
3	Croscarmellose Sodium	USP/ NF	Disintegrant	0.91	2.90	17.40
4	Pregelatinized Starch	USP	Binder	3.75	12.00	72.00
	Granulation :					
5	Sodium Lauryl Sulphate	IP	Wetting agent	0.20	0.64	3.84
6	Purified water	USP/EP /BP/IP/ IH	Granulating fluid	Qs	Qs	600.00
	Dried sized granules weight				**296.60**	**1779.60**

Lot B: Granulation

S. No	Ingredients	Spec.	Function	%w/w	Qty Tab. (In mg)	Qty./ Batch (g)
	Dry mix:					
1	Azithromycin (as dihydrate)	USP	Active	81.88	262.00	1572.00[$]
2	Microcrystalline cellulose	IP	Diluent	5.96	19.06	114.36[$]
3	Croscarmellose Sodium	USP/ NF	Disintegrant	0.91	2.90	17.40
4	Pregelatinized Starch	USP	Binder	3.75	12.00	72.00
	Granulation :					
5	Sodium Lauryl Sulphate	IP	Wetting agent	0.20	0.64	3.84
6	Purified water	USP/EP BP/IP/ IH	Granulating fluid	Qs	Qs	600.00
	Dried sized granules weight				**296.60**	**1779.60**

	Blending of Lot A and Lot B :			**296.60**	**3559.20**
	Lubrication :				
7	Croscarmellose Sodium	USP /NF	1.50	5.80	69.60
8	Silicon Dioxide (Syloid 244 FP)	USP -NF	1.81	4.80	57.60
9	Magnesium Stearate	IP	1.50	4.80	57.60
	Core tablet weight		**97.50**	**312.00**	**3744.00**
	Coating Ingredients@ :				
10	Hydroxyl Propyl Methyl Cellulose (6cps)	IP	1.89	6.05	116.16
11	PEG -6000	IP	0.27	0.85	16.32
12	Talc	IP	0.16	0.50	9.60
13	Titanium dioxide	IP	0.16	0.50	9.60
14	Quinoline yellow	IH	0.03	0.10	1.92
15	Purified water	USP /EP BP/IP/ IH	Qs	Qs	1382.0
	Coated tablet weight		**100.00**	**320.00**	**3840.00**

Note:

$ Quantity of Azithromycin (as dihydrate) USP taken considering 100% assay on as such basis, its quantity to be adjusted with Microcrystalline cellulose IP.

@ 60 % extra coating solution to be prepared to compensate loss during coating 262.00 mg of Azithromycin USP (as dihydrate) equivalent to 250.00 mg Azithromycin anhydrous.

6.11.2 Formula Calculation:

For each Lot:

Qty of Azithromycin dihydrate USP

$$\text{Required (Q)} = \frac{1500.00 \times 100 \times 100}{A \times (100 - W)} \text{ gm}$$

Where A= Assay of Azithromycin dihydrate on anhydrous basis in %.

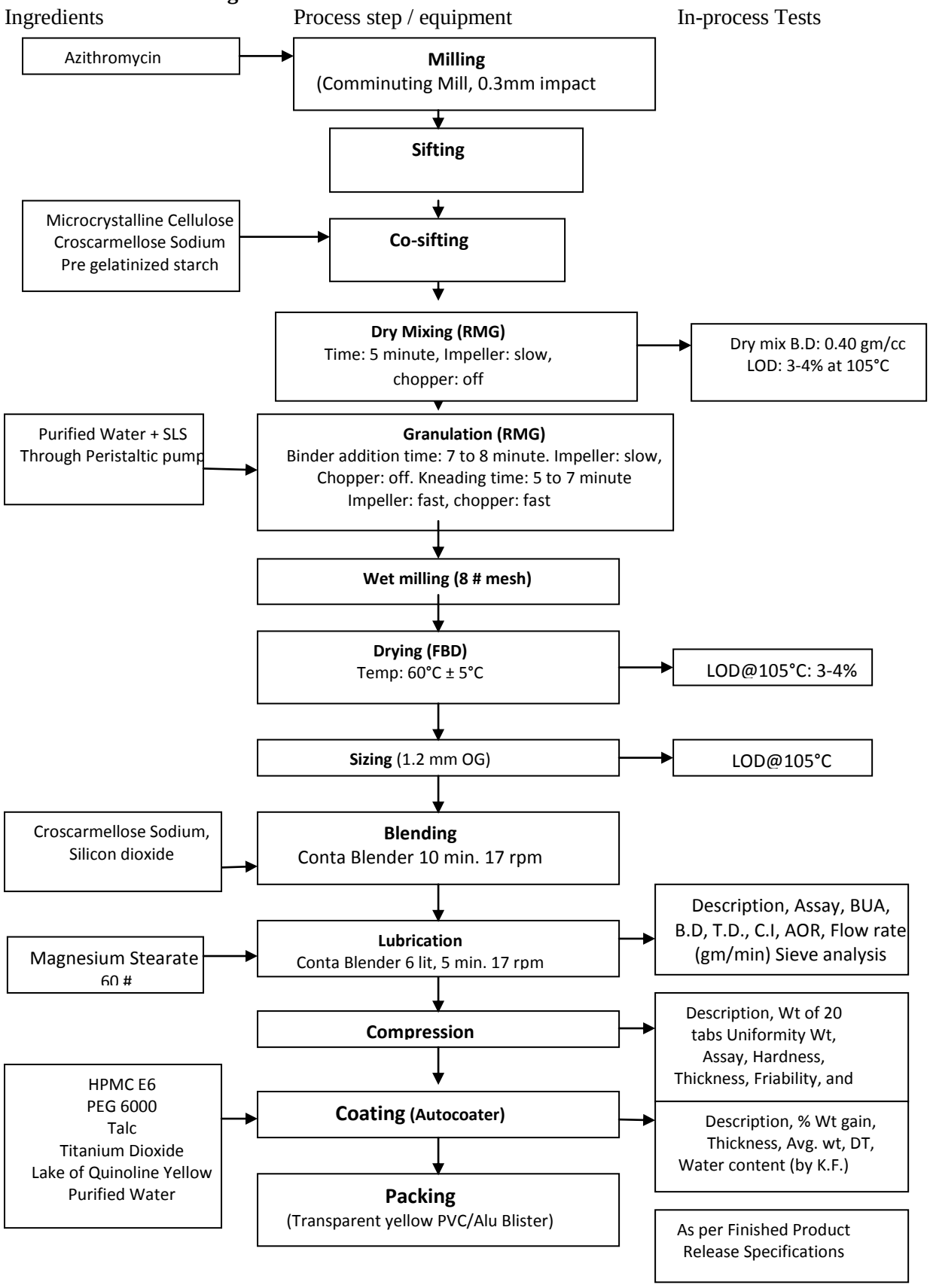
W= water by K.F. in % w/w

Quantity of Microcrystalline cellulose IP required:

= 114.36gm – (Q – 1572.00) gm

Remark: Record B. No., Assay (anhydrous basis) & water by K.F. of API used.

6.11.3 Process Flow Diagram-Schematic:



6.11.13 complete analysis of core tablets:

Sr.No	**Test**	**Limit**	**250 mg**
1	Description	White,round,biconvex tablet, plain on both side	
2	Average weight	312.0±3%	312.00
3	Assay Optimum Hardness	115 N ± 20 N	100.0 %
4	Related Substances (Optimum Hardness) Single Max impurity Total impurities	To be monitored	0.74% 1.78%
5.	Dissolution (45 min)	pH 6.0,phosphate buffer,600 mg trypsin added,900 ml/paddle/100 rpm/time point:45 min	
	Optimum Hardness Low Hardness High Hardness	NLT 75%(D)	98.4 (2.68) 92.3 (1.5) 99.5 (1.49)

6.11.14 complete analysis of coated tablets:

Sr.No	**Test**	**Limit**	**250 mg**
1	Description	yellow,round,biconvex tablet, plain on both side	
2	Average weight	320.0±3%	320.00
3	Assay optimum hardness	----	 98.7 %
4	Related Substances (optimum hardness) Single Max impurity Total impurities	 To be monitored	 0.94% 1.89%
5.	Dissolution	pH 6.0,phosphate buffer,600 mg trypsin added,900 ml/paddle/100 rpm/time point:45 min	
6	% Drug Release (45 min) optimum hardness (RSD)	 NLT 75%(D)	 99.8 (1.43)

6.11.15 Conclusion/Recommendation

1. Water addition rate should be control with peristaltic pump with in binder addition time period as Mentioned**.**

2. Granulation should be perform with slow addition of binder solution and kneading with impeller slow & chopper off to get desired granule characteristics.

2. Wet milling should be performed after granulation.

3. Drying should not perform at more than 55±5°C temp.

4. During coating product temp should not be more than 40°C± 5°C

6.11.16 Stability study

Demo Batch

Batch No – Demo batch Packing – Yellow PVC blister B. Size – 12000 tablet				**Storage condition**	
				40 °C, 75 % RH	
Sr. No	**Tests**	**Specification**	**Initial**	**1 month**	**2 month**
1	Description	Yellow colored, round shaped, biconvex, coated tablet, plain on both side.	complies	Complies	complies
2	**Assay (%)**	**90 % to 110 % of label claim**	**99.7**	**99.2**	**100.1**
3	**Water content (%)**	**To record**	**5.12**	**5.32**	**5.40**
4	**Disintegration time**	**Not more than 30 minutes**	**1.56**	**1.30**	**2.45**
5	**Dissolution at pH 6.0 phosphate buffer**	**Not less than 75 % (D) in 45 minutes**	**95.2 (0.58)**	**99.4 9 (0.85)**	**100.6 (2.08)**

Observation: Stability data show that drug product is stable upto 2 month in accelerated condition

Batch No – Demo batch **Packing – Yellow PVC blister** **B. Size – 12000 tablet**				**Storage condition** **30 °C, 75 % RH**	
S. No	**Tests**	**Specification**	**Initial**	**1 month**	**2 month**
1	Description	Yellow colored, round shaped, biconvex, coated tablet, plain on both side.	**complies**	**Complies**	**complies**
2	**Assay (%)**	**90 % to 110 % of label claim**	**99.7**	**99.5**	**98.8**
3	**Water content (%)**	**To record**	**5.12**	**5.42**	**5.6**
4	**Disintegration time**	**Not more than 30 minutes**	**1.56**	**2.00**	**2.00**
5	**Dissolution at pH 6.0 phosphate buffer**	**Not less than 75 % (D) in 45 minutes**	**95.2(0.58)**	**97.6**	**97.5**

Observation: Stability data show that drug product is stable upto 2 month in intermediate condition.

Batch No – Demo batch **B. Size – 12000 tablet**		**Packing – Yellow PVC blister**		**Storage condition** **25°C, 60 % RH**	
S. No	**Tests**	**Specification**	**Initial**	**1 month**	**2 month**
1	Description	Yellow colored, round shaped, biconvex, coated tablet, plain on both side.	**complies**	**Complies**	**complies**
2	**Assay (%)**	**90 % to 110 % of label claim**	**99.7**	**99.9**	**100.0**
3	**Water content (%)**	**To record**	**5.12**	**5.28**	**5.30**
4	**Disintegration time**	**Not more than 30 minutes**	**1.56**	**2.00**	**2.10**
5	**Dissolution at pH 6.0 phosphate buffer**	**Not less than 75 % (D) in 45 minutes**	**95.2(0.58)**	**96**	**97.23**

Observation: Stability data show that drug product is stable upto 2 month in normal condition

6.11.4 Processing steps:

Process Stage	Critical Process Parameter	Expected Response	Observed Response	Remarks	Proposed Specifications
Lot A granulation					
API milling	0.3 mm screen, impact forward, fast speed in cad mill	0.3 mm screen, impact forward, fast speed in cad mill	0.3 mm screen, impact forward, fast speed in cad mill	Satisfactory	0.3 mm screen, impact forward, fast speed in cad mill
Granulation	1.Binder Addition Time(Peristaltic pump rate) 2.Kneading Time	6-8 Minutes 5 to 7 Minutes (fast-fast)	4 min 30 sec 7 min (impeller slow chopper off)	Satisfactory (Kneading parameter have to changed to get desire granules consistency)	6-8 Minutes 5 to 7 min (impeller slow, chopper off)
Wet milling	8 # sieve	8 # sieve	8 # sieve	Satisfactory	12.7 mm Co- mill
Drying	LOD@105°C	3.0% to 4.0%	4.56%	Dry mix LOD was 5.0%	3.5% to 5.0%
Sizing	1.2 mm screen on horizontal O.G.	1.2 mm screen on horizontal O.G.	1.2 mm screen on horizontal O.G.,	Satisfactory	1.2 mm screen on horizontal O.G.
Lot B granulation					
Granulation	1.Binder Addition Time(Peristaltic pump rate) 2.Kneading Time	6-8 Minutes 5 to 7 Minutes	7 min (30 ml/min) 7 min	Satisfactory	6-8 Minutes 5 to 7 min (impeller slow, chopper off)
Wet milling	8 # sieve	8 # sieve	8 # sieve	Satisfactory	12.7 mm Co- mill
Drying	LOD@105°C	3.0% to 4.0%	4.62 %	Dry mix LOD was 4.68 %	3.5% to 5.0%
Sizing	1.2 mm screen on horizontal O.G.	1.2 mm screen on horizontal O.G.	1.2 mm screen on horizontal O.G.	Satisfactory	1.2 mm screen on horizontal O.G.
Blending of Lot A & B	10 min.	10 minutes	10 minutes	Satisfactory	10 minutes
Blending	10 min.	10 minutes	10 minutes	Satisfactory	10 minutes
Lubrication	5 min.	5 min.	5 min.	Satisfactory	5 min.
Granulometry	Bulk Density Tapped Density Sieve Analysis	To be recorded To be recorded To be recorded	0.47 0.58	Satisfactory Satisfactory Satisfactory	To be recorded To be recorded To be recorded

Compression : For 250 mg strength:				
Avg weight	312.00 ± 3%	312.16 mg	Satisfactory	312.00 ± 3%
Thickness	5.00 ± 0.3 mm	5.10 mm	Satisfactory	5.00 ± 0.3 mm
Hardness	(115±20 N)	125 N	Satisfactory	(115±20 N)
Friability	NMT 1.0%	0.1 %	Satisfactory	NMT 1.0%
D.T.	NMT 15 min	1 min 23 sec	Satisfactory	NMT 15 min
Coating : For 250 mg strength:				
Inlet temp	60 ± 5° C	60 ± 5° C	Satisfactory	55 ± 5 °C
Product temp	45 ± 5 °C	40 ± 5 °C	Satisfactory	40 ± 5 °C
Pan RPM	2-4	2-4	Satisfactory	2-4

6.11.5 Ingredients and sieve used:

Sr. No.	**Ingredients**	**Code**	**Screen Size**	**Remarks**
1	Azithromycin dehydrate	1000494	80#	Satisfactory
2	Microcrystalline cellulose	2000185	40#	Satisfactory
3	Pregelatinized starch	2000227	40#	Satisfactory
4	Croscarmellose sodium	2000054	40#	Satisfactory
5	Silicon dioxide	2000446	40#	Satisfactory
6	Magnesium Stearate	2000156	60#	Satisfactory

The above API was co-sifted with dry mix excipients sifted on vibratory sifter.

Description: White to off-white granular powder.

6.11.6 Dry mix blends analysis:

Sr. No.	Parameter	Results
1	Dry mix : Time	5 minutes
2	B.D.	0.41 gm/cc
3	LOD AT 105°C	4.68%

6.11.7 Details of the blend characteristics after sizing:

Sr. No	Parameter	Lot A	Lot B
1	Description	White to off-white granular powder	White to off-white granular powder
2	B.D	0.47 gm/cc	0.46 gm/cc
3	T.D	0.57 gm/cc	0.55 gm/cc
4	C.I	17.39	14.66
5	H.R.	1.23	1.19
6	AOR	24.3°	23.7°
7	Flow rate (Erveka flow meter, 15.0 mm funnel)	10.6 sec/100 gm	9.8 sec/100 gm
8	Particle size distribution	% wt retain	% wt retain
	#20 retain	1.44	3.52
	#20-#30	7.9	5.34
	#30-#40	8.32	12.06
	#40-#60	18.56	16.42
	#60-#80	19.58	19.68
	#80-#100	16.34	16.20
	Pass through # 100	27.32	24.20
9	Assay	96.7 %	98.2 %
10	Related Impurities Single Max Impurity Total Impurities	 0.83 % 1.88 %	 0.72 % 1.95 %

6.11.8 Details of the lubrication:

Blending with Croscarmellose sodium & Silicon Dioxide: 10 minutes

Lubrication with Magnesium stearate: 5 minutes in conta blender at 17 rpm

Inference: 10 min with Croscarmellose sodium & Silicon Dioxide then 5 min with Magnesium stearate is sufficient**.**

6.11.9 Final blend characteristics:

Sr. No.	Parameter	Results
1	Description	White to off-white coloured granular powder
2	LOD@105°C	4.78%
3	Bulk density	0.49 gm/cc
4	Tapped density	0.62 gm/cc
5	Hausner's ratio	1.27
6	Compressibility Index	21.37%
7	Angle of repose	24.8°
8	Flow rate (Erveka flow meter, 15.0 mm funnel)	8.5 sec/100 gm
9	Particle size distribution	% Retain
	#20 retain	2.6
	#20-#40	18.1
	#40-#60	17.45
	#60-#80	17.10
	#80-#100	11.70
	Pass through # 100	33.00
10	Blend uniformity	
	S-1	**98.4**
	S-2	97.5
	S-3	98.9
	S-4	97.2
	S-5	99.4
	S-6	98.8
	S-7	97.8
	MEAN	**98.3**
11	Composite	101.8
12	Related Impurities Single Max Impurity Total Impurities	 0.52% 0.52%

Inference: Lubricated blend is found satisfactory in terms of flow and particle size distribution

6.11.10 compressions:

S.No.	Parameters	Observation
		250 mg
01	Machine Name	Cad mach rotary compression machine 20 station
02	Machine rpm	25
03	Punch description	12/32" Circular Biconvex, Plain/Plain (D tooling) punches plain on both the sides.
04	No. of punch sets	2 sets
05	Machine run time	3 hr

6.11.11 Compression parameters:

Batch no.		**Demo**
Dimension		12/32"
U/P		plain
L/P		plain
Tooling		D
Low hardness	Average weight (mg) 312.0 ± 3 % (302.64 to 321.36 mg)	311.39mg (308.0 mg to 314.0 mg)
Optimum hardness		312.16mg (311.6 mg to 313.0 mg)
High hardness		308.2mg (306.8 mg to 309.5mg)
Low hardness	Hardness 115 N ± 20 N (95 N to 135 N)	63.70N (61 N to 75 N)
Optimum hardness		125.10N (113 N to 140 N)
High hardness		165.60N (138 N to 182 N)
Low hardness	Thickness 5.00 ± 0.3 mm (4.70 to 5.30 mm)	5.29mm (5.21 mm to 5.39 mm)
Optimum hardness0		5.10mm (4.96 mm to 5.31 mm)
High hardness		4.82mm (4.78 mm to 4.87 mm)
Low hardness	DT NMT 15 mins.	54 sec
Optimum hardness		1.0 min 40 sec
High hardness		3.0 min 10 sec
Low hardness	Friability %w/w NMT 1.0 % w/w	100R-0.28 200R–0.39% 300 R - 0.46 %
Optimum hardness		100R-0.1% 200R-0.27% 300 R - 0.37 %
High hardness		100R-0.20% 200R-0.26% 300 R - 0.41 %

6.11.12 Coating parameters: 250 mg

Time	Inlet Temp	Product temp	Pan rpm	Spray rpm	Spray rate
12:05	56	40	1	-	-
12:15	57	40	1	-	-
12:17	57	38	2	2	3
12:25	62	39	3	3	5
12:30	60	39	3	3	6
12:40	67	39	3	4	6
12:45	66	40	3	5	6
12:55	66	38	3	3	6
13:05	63	37	3	3	5
13:15	64	37	3	3	5
13:25	45	35	2	-	-

Product Composition:

Granulation lot A & Lot B

S. No	Item code	Ingredients	Spec. *	Function	%w/w	Qty /Tab. (In mg)	Qty./batch (In kg)
	Dry mix:						
1	1000494	Azithromycin (as dihydrate)	USP	Active	81.88	262.00	19.65$
2	1000494	Azithromycin (as dihydrate)	USP	Active	--	--	0.20#
3	2000185	Microcrystalline cellulose	IP	Diluent	5.96	19.06	1.43$
4	2000054	Croscarmellose Sodium	USP/NF	Disintegrant	0.91	2.90	0.218
5	2000227	Pregelatinized Starch	USP	Binder	3.75	12.00	0.900
	Granulation :						
6	2000329	Sodium Lauryl Sulphate	IP	Wetting agent	0.20	0.64	0.048
7	1822352	Purified water	USP/Ph.Eur/BP/IP/IH	Granulating fluid	Qs	Qs	7.500**
	Dried sized granules weight					**296.60**	**22.246**

S. No	Item code	Ingredients	Spec.*	%w/w	Qty /Tab. (In mg)	Qty./batch (In kg)
	Blending of Lot A and Lot B :				**296.60**	**44.492**
	Lubrication :					
8	2000054	Croscarmellose Sodium	USP /NF	1.81	5.80	0.870
9	2000446	Silicon Dioxide (Syloid 244 FP)	USP -NF	1.50	4.80	0.720
10	2000156	Magnesium Stearate	IP	1.50	4.80	0.720
	Core tablet weight			**97.50**	**312.00**	**46.802**
Coating Ingredients@ :						
11	2000115	Hydroxyl Propyl Methyl Cellulose (6cps)	IP	1.89	6.05	1.452
12	2000198	PEG -6000	IP	0.27	0.85	0.204
13	2000352	Talc	IP	0.16	0.50	0.120
14	2000358	Titanium dioxide	IP	0.16	0.50	0.120
15	2000241	Quinoline yellow	IH	0.03	0.10	0.024
16	1822352	Purified water	USP/Ph. Eur/BP/IP/IH	Qs	Qs	17.280**
	Coated tablet weight			**100.00**	**320.00**	**48.000**

Note:

* Always current version of specification should be followed

$ Quantity of Azithromycin (as dihydrate) USP taken considering 100% assay on As such basis, its quantity to be adjusted with microcrystalline cellulose IP

\# 1.0% w/w extra API to be dispensed to compensate for milling loss and 19.65 kg milled API with assay compensation is to be used for the further processing. The excess API, if Any, is to be discarded after milling.

@ 60 % extra coating solution to be prepared to compensate loss during coating

****** Removed during process, does not remain in the finished product

262.00 mg of Azithromycin USP (as dihydrate) equivalent to 250.00 mg Azithromycin Anhydrous.

Formula Calculation:

7.1 Calculation for actual quantity of Azithromycin dihydrate USP:

For each Lot:

Actual Quantity of Azithromycin dihydrate USP Required in kg **(Q)** per batch = **Assay on anhydrous basis** $\frac{18.75 \times 100 \times 100}{A \times (100 - W)}$ or **Assay on as is basis** $\frac{18.75 \times 100}{B}$

Where:

A = Assay of Azithromycin USP on anhydrous basis in % w/w

B = Assay of Azithromycin USP on as is basis in %w/w

W= water by KF in % w/w

7.2 Calculation for actual quantity of microcrystalline cellulose IP

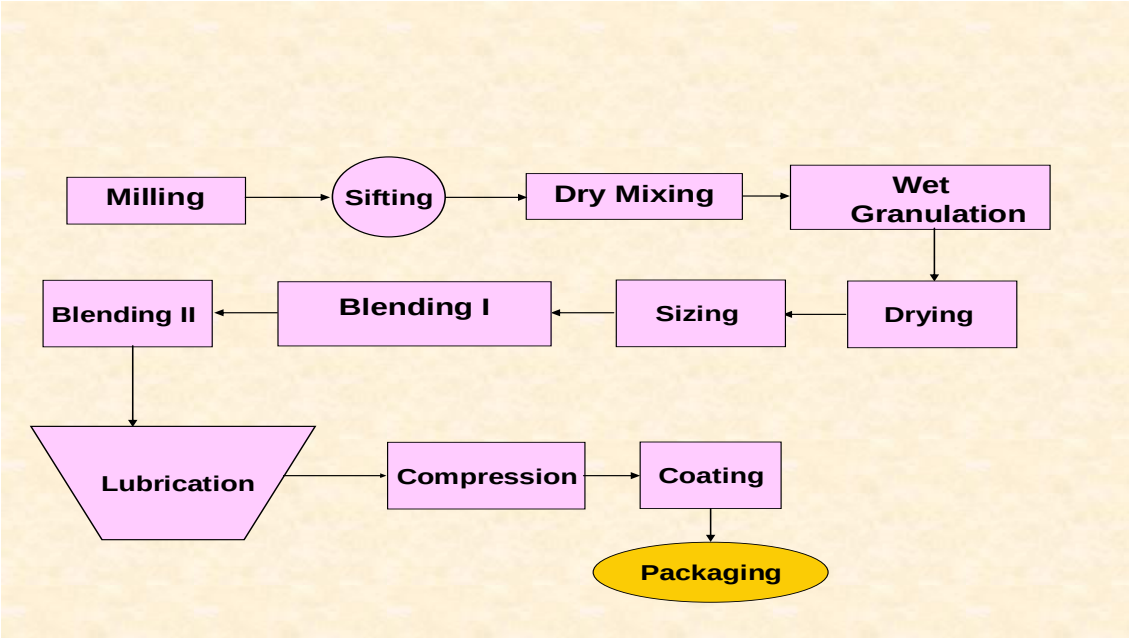
(Depending upon 3.1.1 and Theoretical Quantity of Microcrystalline cellulose IP)

Actual Quantity of Microcrystalline cellulose IP required per batch in kg **(P)** = $1.43 - (Q - 19.65)$

Note:

API of multiple A.R. No's may be used for which assay calculation has to be done accordingly

Process Flow Diagram-Schematic:


Milling
Sifting
Dry Mixing
Wet Granulation
Drying
Sizing
Blending I
Blending II
Lubrication
Compression
Coating
Packaging

7.3 Manufacturing conditions and Precautions:

Ensure that all the area is cleaned and free from previous product material before taking any batch

Ensure that all the input materials used in a batch bear QA approved labels.

Ensure that all the personals in the manufacturing area wear protective clothing.

Ensure that the Room Temperature is NMT 27°C and Relative humidity is below 60 % RH.

Ensure that all the activities are carried out as per MFC and recorded in the BMR.

7.3.1 Manufacturing Process:

7.3.2 Milling of API: Mill the Azithromycin dihydrate USP through 0.3mm screen impact Forward at fast speed in Cadmill.

7.3.3 Dispensing:

Check all the dispensed ingredients as per the material requisition note and record in BMR.

7.3.4 Sifting

1 Sift the calculated quantity of milled API through 80 # mesh on Vibratory sifter.

2 Co-sift the calculated quantity of Microcrystalline cellulose IP, Croscarmellose sodium USP-NF 0.218 kg and Pregelatinized starch USP 0.900 kg with API of step 7.3.1 through 40# on vibratory sifter

7.3.5 **Dry Mixing**

Load the sifted materials from step 9.4.3 into a clean and dry Rapid Mixer Granulator fitted with co-mill having 8.0 mm SS Screen and mix for 5 minutes with Chopper off and impeller at slow speed.

Sampling locations in Rapid mixer Granulator:

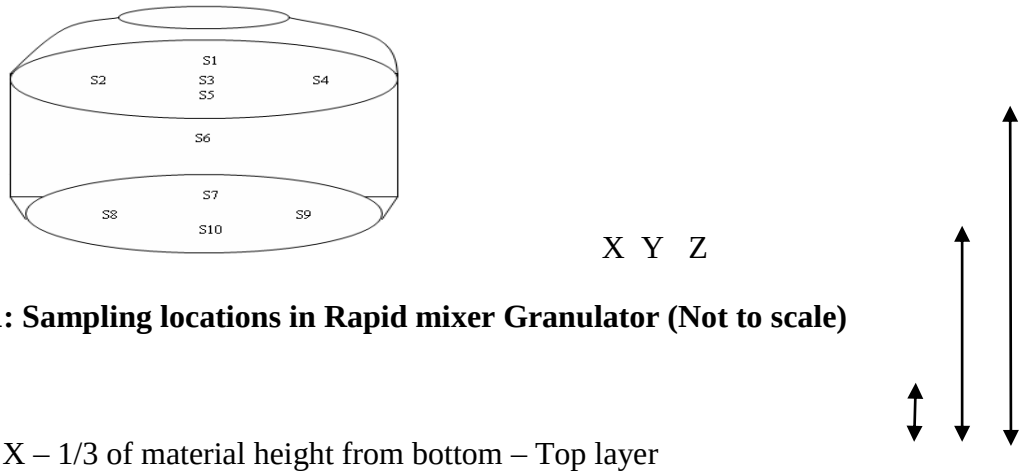


Figure No. 8.1: Sampling locations in Rapid mixer Granulator (Not to scale)

X – 1/3 of material height from bottom – Top layer

Y – 1/2 of material height from bottom – Middle layer

Z – 2/3 of material height from bottom – Bottom layer

S1 –Upper –Rear	**S6 – Middle– Center**
S2 - Upper –Left	**S7-Lower – Rear**
S3 – Upper – Center	**S8 – Lower – Left**
S4 – Upper - Right	**S9 – Lower – Right**
S5 – Upper- Front	**S10 – Lower – Front**

7.3.6 Granulation

1) Binder solution preparation

Dissolve Sodium Lauryl Sulphate IP 0.048 kg in 7.500 kg of purified water USP/Ph.

Eur/BP/IP/IH to get a clear solution.

2) Binder Solution Additions

Add binder solution prepared at step 7.5.1 to the dry mixed of step 7.4 by using peristaltic

Pump in Rapid Mixer Granulator fitted with co-mill having 8.0 mm SS Screen with

Impeller at slow speed and Chopper off in 6 to 8 min.

3) Kneading

Carry out kneading for 4 to 7 minutes at impeller slow and chopper off. If required, add

Extra amount of Purified water USP/Ph.Eur/BP/IP/IH to get the desired consistency of wet

Mass. Record the extra quantity added in BMR.Unload the wet mass (Granules) through

Co-mill using 8.0 mm SS Screen.

7.3.7 Drying

Dry the wet mass of Step of 7.5.3 at inlet air temperature 55 ± 5°C to get LOD 3.5% to

5.0% w/w at 105°C.

7.3.8 Sizing:

Pass the dried granules of step 7.6 through Oscillating granulator fitted with 1.2 mm SS

Screen. Collect the granules into clean & dry suitable container.

Theoretical Yield = 22.246 kg

Lot B: Granulation

Manufacturing Process: for Lot B: Granulation

Repeat the manufacturing process same as steps 9.1 to 9.7

7.3.9 Blending I of Lot A and Lot B:

Blending the Lot A and Lot B sized granules in Bunker with Conta blender for 10 min.

7.4 Blending – II:

7.4.1 Sift 0.870 kg of Croscarmellose sodium USP/NF and 0.720 kg Silicon Dioxide USP-NF (Syloid 244 FP) through 40# sieve on vibratory sifter.

7.4.2 Blend the granules of step 7.8 with Croscarmellose sodium USP/NF and Silicon Dioxide (Syloid 244 FP) USP-NF for 10 minutes in Bunker with Conta blender.

7.5 Lubrication:

7.5.1 Sift 0.720 kg of Magnesium Stearate IP through 60# sieves on vibratory sifter then blend With material of step 7.9.2 for 5 minutes

7.5.2 Send the sample of blend material to Q.C along with sample test request slip for Analysis.

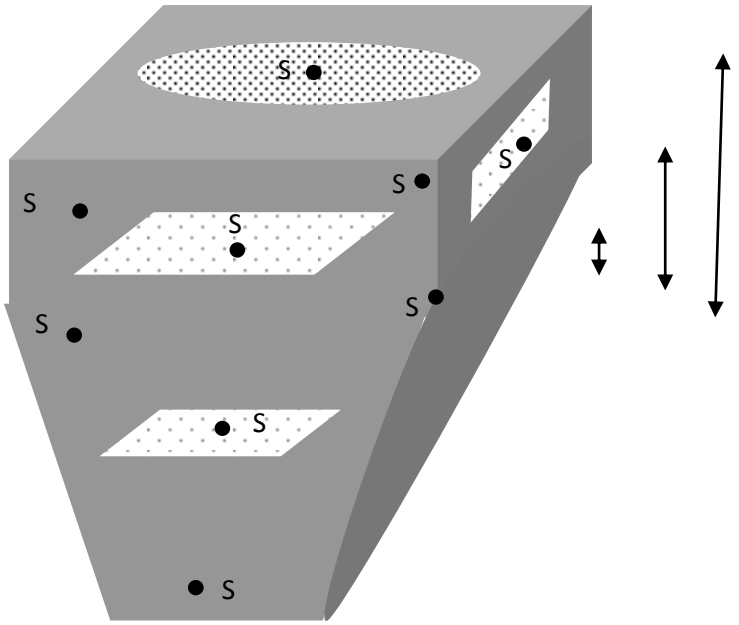
7.5.3 Weight and record the yield of the blend in BMR.

Theoretical Yield: 46.802 kg

Sampling Instruction:

Insert the unit dose sampler at an angle of 45-60^0 in closed position, such that the slot is facing upwards at the nearest locations identified in the figure.

Figure No. 7.2: Sampling locations in Conta Blender (Not to scale)



X – 2/3 of material height from bottom – Upper layer

Y – 1/2 of material height from bottom – Middle layer

Z -- 1/3 of material height from bottom – Lower layer

7.6 Compression:

7.6.1. Conmpress the granules into tabalets on rotary compression machine using 12/32" SC, plain /Plain (D tooling) punches plain on both sides

7.6.2 Check Description, Weight of 20 tablets, Average weight, Uniformity of weight Hardness, Friability, Thickness, Disintegration time & record these parameters in BMR.

7.6.3. Send the sample of compressed tablets to QC along with sample test request slip for analysis Weigh and record the weight of compressed tablets in BMR.

Theoretical yield = 46.802 kg

7.7 Coating

Preparation of Film coating suspension:

7.7.1 Take 10.00 kg Purified Water USP/Ph.Eur/BP/IP/IH in a SS tank and slowly add 1.452 kg Hydroxyl Propyl Methyl Cellu. (6cps) IP into it while stirring. Stir continuously till Clear Solution is obtained.

7.7.2 Take 5.00 kg of Purified Water USP/Ph.Eur/BP/IP/IH. Disperse 0.120 kg Titanium Dioxide IP and 0.120 kg Talc IP and 0.024 kg of Quinoline yellow IH mill it in colloidal Mill for 20 min. Rinse the colloid mill with Purified water USP/Ph.Eur/BP/IP/IH

7.7.3 Add suspension of step 7.12.2 in solution of step 7.12.1 with continuous stirring.

7.7.4 Dissolve 0.204 kg PEG 6000 IP in purified water USP/Ph.Eur/BP/IP/IH and add in to Coating suspension of step 7.12.3. Continue the stirring for 10 minutes.

7.7.5 Filter the coating solution through 100#.

7.7.6 Drying/Heating of Tablets

Stage	Inlet Temp. (°C)	Duration (min)	Pan RPM
Before Coating	55 ± 5	10	Inching
After 100% Coating	40 ± 5	10	Inching

7.7.5 Coating parameters:

Sr. No.	Parameter	Limit
01.	Inlet air temperature	55.0 °C ± 5.0°C
02.	Exhaust temperature	To be established
03.	Pan R.P.M.	To be established
04.	Spray rate	To be established
05.	Atomization air pressure	To be established
06.	Product temperature	40 ± 5°C
07.	Spraying gun nozzle Diameter	1.2 mm

7.8 Coating Process:

7.8.1 Prior to loading the tablets in coating pan, record average mass (A) of 50 tablets.

7.8.2 Spray the coating suspension on the tablets in pan according to conditions given above till required weight gain is achieved. After completion of coating process, allow the tablets to dry in the pan in inching mode for 10 minutes in a stream of air temperature at 40°C ±5°C.

7.8.3 Record the average mass of coated tablets in the BMR. Weight gain should be 2.5 $\pm$ 0.5% w/w on the average mass (A).

7.8.4 Unload the coated tablets in to a clean double polypropylene lined container. Weigh and record the weight of coated tablets in BMR.

7.8.5 Send the sample of coated tablets along with Test Request Form to QC dept.for analysis as per finish product release specification.

Theoretical yield = 48.000 kg

7.8.6 On receipt of QA/QC approval, send the tablets for packing.

7.9. In process test parameters:

Stage	Test	Acceptance Criteria
Drying	LOD	3.5 – 5.0 %w/w at 105°C
Lubrication	Description	White to off-white granular powder
	Water Content	NMT 6.0%w/w
	Assay	Not less than 95.0 % and not more than 105.0% of labeled amount of Azithromycin.
Compression	Description	White to off-white, round biconvex, uncoated tablets plain on both sides
	Average weight	312.0 mg ± 3% (302.6 mg to 321.3 mg)
	Weight of 20 tablets	6.24 g ± 3% (6.05g to 6.43 g)
	Uniformity of weight	Average weight ± 5 %
	Hardness	115 N ± 40 N (75 N to 155 N)
	Disintegration time	Not more than 15 min
	Friability	Not more than 1% w/w
	Thickness	5.00 ± 0.30 mm (4.70 mm to 5.30 mm)
	Dissolution	Not less than 75 % (D) of the labeled amounts of Azithromycin dissolved in 45 minutes.
	Assay	Not less than 95.0% and not more than 105.0% of the labeled amounts of Azithromycin
	Water content	NMT 6.0%w/w
Coating*	Description	Yellow colored, round biconvex, film coated tablets plain on both sides
	Thickness	5.10 ± 0.30 mm (4.80 mm to 5.40 mm)
	Theoretical weight	320.0 mg
	Avg. Weight	320.0 mg ± 3 % (310.4 mg to 329.6 mg)
	% Wt. gain	2.50% ± 0.5%
	Disintegration Time	Not more than 30 min.
	Uniformity of Weight	Not more than two of the individual weights deviates from the average weight by more than 5% and none deviates by more than 10%

*** Remaining tests to comply as per the finished product release specification.**

7.10 Yield Statement:

Sr. No.	Stage	Theoretical Yield
1.	Lubricated granules	46.802 kg
2.	After Compression	46.802 kg
3.	After Coating	48.000 kg

CHAPTER - 8

RESULTS AND DISCUSSION

8.1 Evaluation of physical parameters of Azithromycin:

8.1.1 Organlopetic Properties:

Test	Specification/Limits	Observations
Color	White or almost white crystalline powder	White crystalline powder
Taste	Bitter	Bitter
Odour	Odourless	Odourless

8.2 Flow Properties (Angle of repose):

Table No 11

Material	Angle of repose
Azithromycin	$32^{o}85$”

8.3 Determination of Densities:

Table No 12

Material	Bulk Density (gm/ml)	Tapped density (gm/Ml)
Gliclazide	0.27	0.35

8.4 Powder compressibility:

Table No 13

Materials	Compressibility index	Hausner ratio
Azithromycin	22.86%	1.30%

8.5 Solubility:

It was determined as per procedure given in method section 5.1.6. The following table illustrated the result

Table No 14

Test	Specification	Result
Solubility in water, alcohol.	Practically insoluble in water Soluble in methanol, ethanol, chloroform, and dimethylchloride	Complies

Assay (by AZIT-IMTB-10-IN**):**

Table No 15

Test	Specification	Observation
Assay	99.0 - 101.0	99.89

8.6 Formulation Compositions:

Table No 23

INGRIDIENT NAME (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Azithromycin	262.00	262.00	262.00	262.00	262.00	262.00
Microcrystalline	19.06	19.06	19.06	19.06	19.06	19.06
Pregelatinized starch	12.00	12.00	12.00	12.00	12.00	12.00
Croscarmellose sodium	2.90	2.90	2.90	2.90	2.90	2.90
Croscarmellose sodium	5.80	5.80	5.80	5.80	5.80	5.80
Colloidal Silicon	4.80	4.80	4.80	4.80	4.80	4.80
Magnesium Stearate	4.80	4.80	4.80	4.80	4.80	4.80
Purified water	QS	QS	QS	QS	QS	QS
Total weight	**312.00**	**312.00**	**312.00**	**312.00**	**312.00**	**312.00**
Coating						
Hydroxyl Propyl Methyl Cellulose (6cps)	6.05	6.05	6.05	6.05	6.05	6.05
PEG -6000	0.85	0.85	0.85	0.85	0.85	0.85
Talc	0.50	0.50	0.50	0.50	0.50	0.50
Titanium dioxide	0.50	0.50	0.50	0.50	0.50	0.50
Quinoline yellow	0.10	0.10	0.10	0.10	0.10	0.10
Purified water	**Qs**	**Qs**	**Qs**	**Qs**	**Qs**	**Qs**
Total weight	**320.00**	**320.00**	**320.00**	**320.00**	**320.00**	**320.00**

8.7 Physical Parameters and Drug Content:

Table No 24

Formul-ations	Weight variation (n=20) (mg ± SD)	Friability (%)	Hardness (Newton)	Disintegration Time (seconds)	Drug content (%)	Thickness (mg ± SD)
F1	312±0.54	0.36	112±20	85±0.7	99.24	3.2±0.009
F2	311±0.91	0.35	113±20	86±0.8	98.16	3.2±0.008
F3	312±0.63	0.41	110±20	85±0.6	98.74	3.2±0.011
F4	312±0.52	0.42	111±20	84±0.6	98.02	3.1±0.010
F5	313±0.49	0.36	112±20	86±0.7	98.21	3.3±0.008
F6	312±0.83	0.37	113±20	87±0.4	99.46	3.2±0.008

The formulated tablets were then evaluated for various physical characteristics like weight variation, friability, hardness, disintegration time, drug content, thickness. The weight variation of tablet was uniform in all formulations and ranged from 312±0.52 to 313±0.49. Friability values were ranged from 0.35 to 0.42. The hardness of prepared tablets was ranged from 110±20 to 113±0.20.disintegration time of tablet values ranged from 84±0.6 to 87±6.3. Drug content of tablets ranged from 98.02 to 99.46 And the thickness values were ranged from 3.1±0.008 to 3.3±0.008.

8.8 Dissolution Data of Tablet Formulation of Azithromycin tablets:

Table No 25

Time (min)	CUMULATIVE PERCENT DRUG RELEASE (%)					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	45.19	49.13	41.05	50.04	46.15	46.72
30	75.61	71.91	70.13	71.19	70.89	71.17
45	91.09	96.94	93.61	99.92	93.22	97.61
60	98.71	99.54	98.76	--	99.07	--

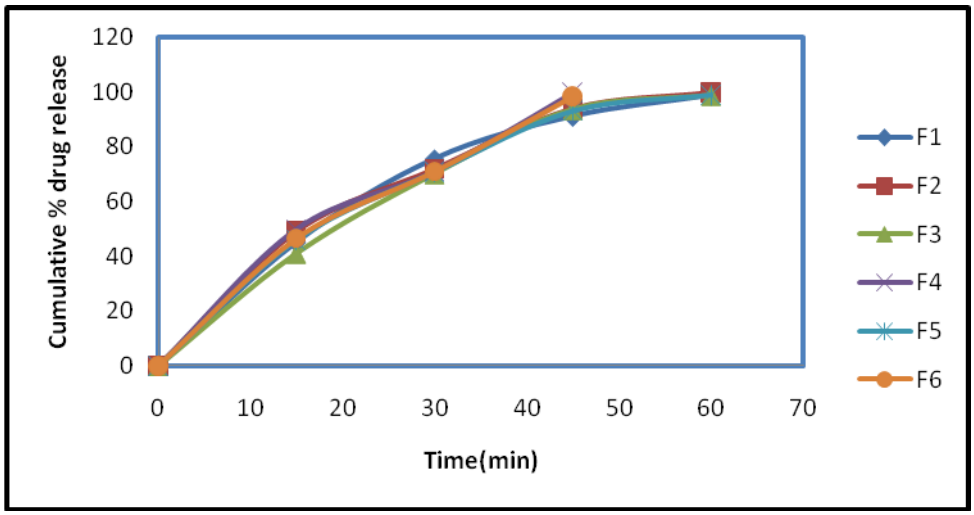


Fig No 13: In-vitro Dissolution Graph of Tablet Formulation of Azithromycin tablets

Dissolution data of Optimized Formulation and Marketed Brand:

8.9 Comparison with the Marketed Product

Table No 26

Time (min)	Mean Cumulative % Drug Release	
	F4	Marketed product
0	0	0
15	50.04	39.63
30	71.19	68.25
45	99.92	93.07
60	--	99.48

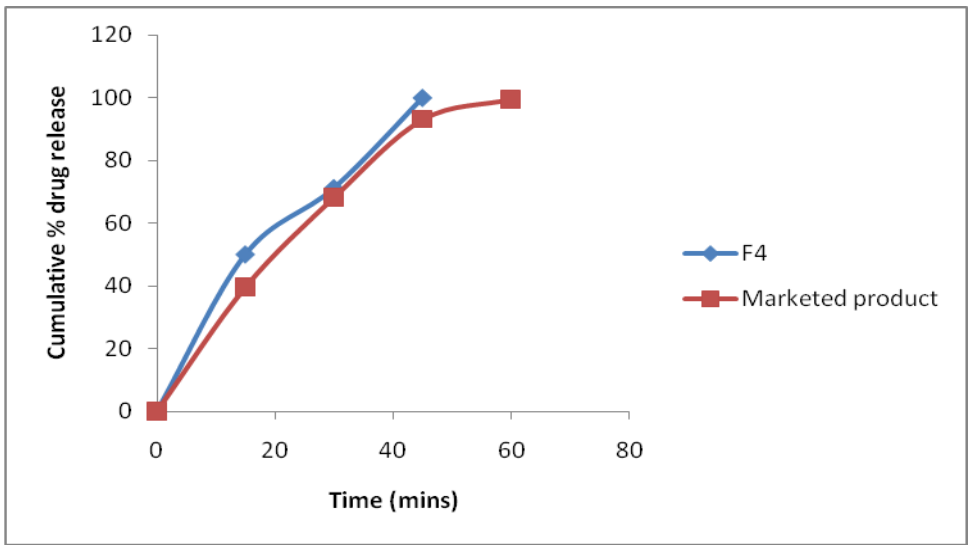


Fig No 14: Comparision with the Marketed Product

8.10 STABILITY STUDIES:

Optimized formulation (F4) was subjected to stability studies at $40^{o}c\pm 2^{o}c/75\%$ RH ±5 % for 2 months. The product was evaluated for appearance and hardness. Drug release studies were conducted as per the planned scheduled as above.

Storage conditions at: $40^{O}C\pm2\ ^{O}C/$ 75 % RH±5%.

Stability studies are evaluated for following parameters

- Hardness
- Friability
- Weight variation
- Drug content
- In-vitro dissolution studies

Descriptions:

Batch No – Demo batch **B. Size – 12000 tablet**		**Packing – Yellow PVC blister**		**Storage condition**	
				40 °C, 75 % RH	
Sr. No	**Tests**	**Specification**	**Initial**	**1 month**	**2 month**
1	Description	Yellow colored, round shaped, biconvex, coated tablet, plain on both side.	complies	Complies	complies
2	**Assay (%)**	**90 % to 110 % of label claim**	**99.7**	**99.2**	**100.1**
3	**Water content (%)**	**To record**	**5.12**	**5.32**	**5.40**
4	**Disintegration time**	**Not more than 30 minutes**	**1.56**	**1.30**	**2.45**
5	**Dissolution at pH 6.0 phosphate buffer**	**Not less than 75 % (D) in 45 minutes**	**95.2 (0.58)**	**99.4 9 (0.85)**	**100.6 (2.08)**

Observation: Stability data show that drug product is stable upto 2 month in accelerated condition

Batch No – Demo batch **B. Size – 12000 tablet**		**Packing – Yellow PVC blister**		**Storage condition**	
				30 °C, 75 % RH	
S. No	**Tests**	**Specification**	**Initial**	**1 month**	**2 month**
1	Description	Yellow colored, round shaped, biconvex, coated tablet, plain on both side.	**complies**	**Complies**	**complies**
2	**Assay (%)**	**90 % to 110 % of label claim**	**99.7**	**99.5**	**98.8**
3	**Water content (%)**	**To record**	**5.12**	**5.42**	**5.6**
4	**Disintegration time**	**Not more than 30 minutes**	**1.56**	**2.00**	**2.00**
5	**Dissolution at pH 6.0 phosphate buffer**	**Not less than 75 % (D) in 45 minutes**	**95.2(0.58)**	**97.6**	**97.5**

Observation: Stability data show that drug product is stable upto 2 month in intermediate condition.

Batch No – Demo batch **B. Size – 12000 tablet**		**Packing – Yellow PVC blister**		**Storage condition**	
				25°C, 60 % RH	
S. No	**Tests**	**Specification**	**Initial**	**1 month**	**2 month**
1	Description	Yellow colored, round shaped, biconvex, coated tablet, plain on both side.	**complies**	**Complies**	**complies**
2	**Assay (%)**	**90 % to 110 % of label claim**	**99.7**	**99.9**	**100.0**
3	**Water content (%)**	**To record**	**5.12**	**5.28**	**5.30**
4	**Disintegration time**	**Not more than 30 minutes**	**1.56**	**2.00**	**2.10**
5	**Dissolution at pH 6.0 phosphate buffer**	**Not less than 75 % (D) in 45 minutes**	**95.2(0.58)**	**96**	**97.23**

Observation: Stability data show that drug product is stable upto 2 month in normal condition

CHAPTER - 9

CONCLUSION

From the present work , it can be concluded that the results suggested that the prepared formulations were stable and globally acceptable. In the wake of patentability of immediate release dosage forms

The results of the present research work gives idea about the formulation of various bacteriostatic drugs as immediate release dosage forms. The research work was done with economical, commercial and regulatory point of view. The final products developed in the research may be commercialized after the establishment of the safety and efficacy in the human volunteers.

In future , with the help of invivo studies reduction is dose is possible, which reduce adverse effect

CHAPTER - 10

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